Striverdi® Respimat® (olodaterol) Inhalation Spray

United States Food and Drug Administration
Pulmonary-Allergy Drugs Advisory Committee

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Boehringer Ingelheim

Introduction

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Boehringer Ingelheim

Unique Features of Olodaterol Respimat®

- A long-acting, once-daily β_2-adrenergic agonist
  - Aqueous formulation
  - Highly selective
- The RESPIMAT inhaler
  - Multi-dose inhaler with dose indicator
  - Slow-moving aerosol cloud to enhance medication inhalation

Characteristics of the Olodaterol Development Program in COPD

Enrolled patients representative of those seen in clinical practice

- Patients with moderate, severe, and very severe COPD
- All patients in Phase III 48-week studies allowed to continue on their usual care, including
  - Short-acting anticholinergics and beta-agonists
  - Long-acting anticholinergics
  - Inhaled corticosteroids
  - Xanthines
- 28 clinical trials, including 4,329 COPD patients, 731 patients with asthma, and 276 healthy volunteers

Olodaterol Phase III Clinical Development

- **10 studies:**
  - 2 pairs of pivotal 48-week studies (N = 3,104)
  - 2 pairs of 6-week bronchodilator profile studies (N = 429)
  - 1 pair of exercise tolerance studies (N= 308)

Phase III studies also provide evidence of benefit in patient-relevant outcomes such as shortness of breath and rescue medication use

What We Will Present Today

- Efficacy: Olodaterol 5 µg qd improved lung function (FEV_1 AUC_{0-3} and trough FEV_1) versus placebo over 48 weeks in patients with moderate to very severe COPD
  - Lung function improvements were evident in all patient sub-groups
  - Clinically meaningful bronchodilation when considered in light of background therapy
  - Rapid onset of action
  - Olodaterol improved exercise tolerance time vs placebo; describes positive effect on functional capacity as a result of airflow improvement
- Safety: No major safety concerns were identified among any patient subgroup or co-medication subgroup

Olodaterol Proposed Indication

- Olodaterol 5 µg, is indicated for
  - The long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema
- Important limitations:
  - NOT indicated to treat acute deterioration of COPD (not for rescue use)
  - NOT indicated to treat asthma

Agenda

COPD Disease Background	**Richard Casaburi, PhD, MD** Professor of Medicine Harbor-UCLA Medical Center
Clinical Efficacy	**Alan Hamilton, PhD** Clinical Program Leader Boehringer Ingelheim
Clinical Safety	**Bernd Disse, MD, PhD** Respiratory – Therapeutic Area Head Boehringer Ingelheim
Clinical Perspective	**Richard Casaburi, PhD, MD** Professor of Medicine Harbor-UCLA Medical Center

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COPD Disease Background

Richard Casaburi, PhD, MD

Professor of Medicine
UCLA School of Medicine
Medical Director, Rehabilitation Clinical Trials Center

Los Angeles Biomedical Research Institute at
Harbor-UCLA Medical Center

The Treatment Approach for COPD Has Evolved Over Time

Previous approach:

Chronic condition characterized by irreversible airflow limitation for which no effective therapy is available

Current optimism:

Preventable and treatable disease state characterized by airflow limitation that is not fully reversible

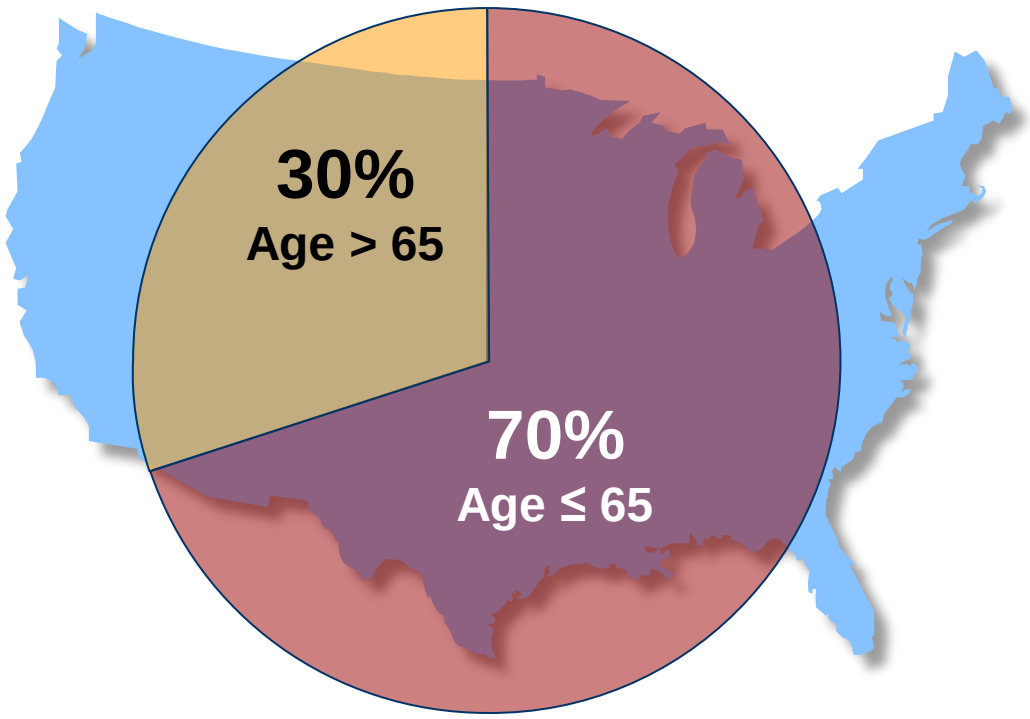
Guidelines definition:

GOLD: "…***preventable and treatable*** disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by ***airflow limitation that is not fully reversible*****.** The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases."[a]

[a] **The Global Initiative for Chronic Obstructive Lung Disease. *GOLD Report—Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease* 2010.**

COPD Is a Critical Health Issue in the United States

Over 14 million diagnosed[a]

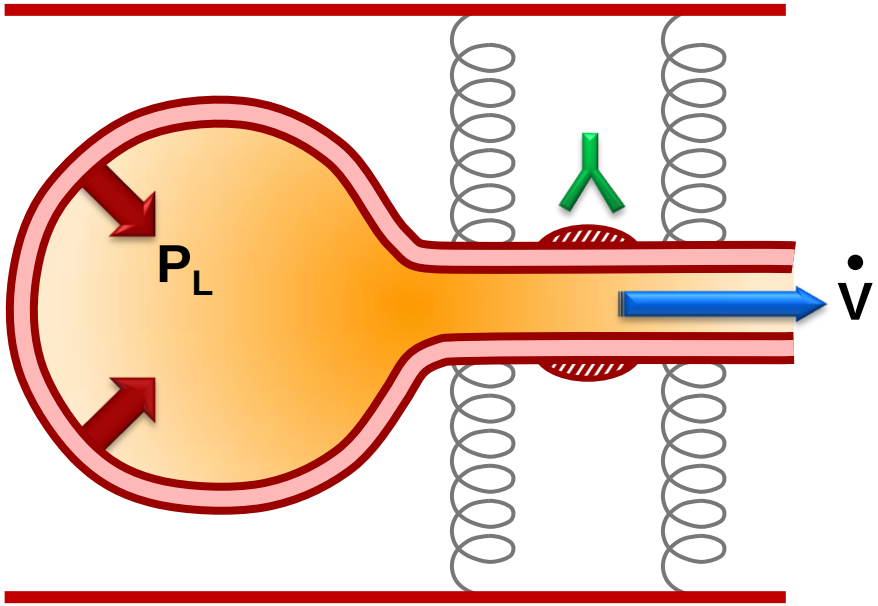


- Approximately 12 million people have undiagnosed COPD[a]
- Third leading cause of death as of 2010[b]
  - With increasing death rates
- ~13.4 million doctor visits, 634,000 hospitalizations, ~$50 billion total costs annually[c,d,e]
- Increasing prevalence and death rate among women[f,g]

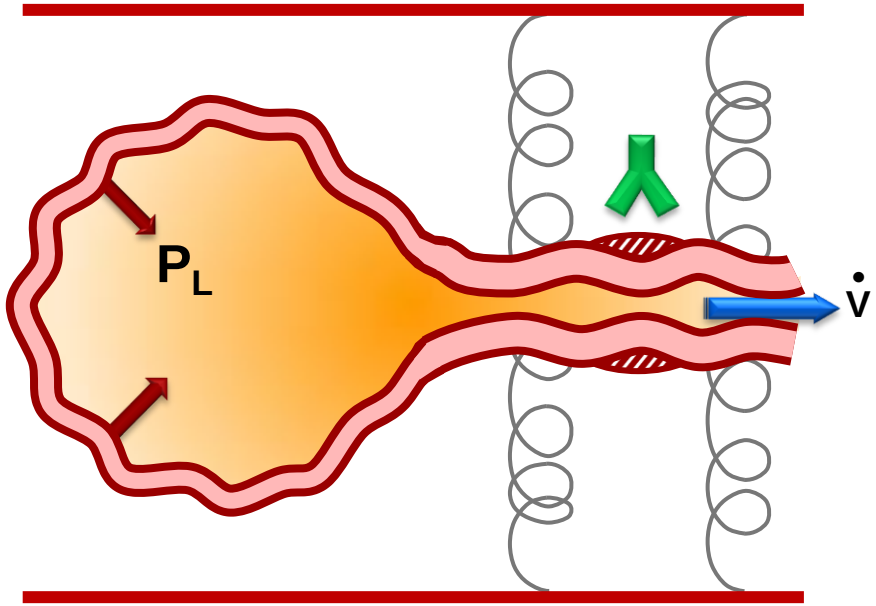
[a] Morbidity and Mortality 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases; [b] Miniño AM, et al. *Nat Vital Stat Report*. 2012; [c] American College of Chest Physicians (ACCP); the Chest Foundation. Living Well With COPD: Chronic Bronchitis and Emphysema Patient Education Guide 2004; [d] Kirsch B. *Managed Care Magazine*. 2011; [e] Morbidity and Mortality 2009 Chart Book on Cardiovascular, Lung, and Blood Diseases; [f] NCHS Data Brief No. 63. Centers for Disease Control and Prevention Web site. Published June 2011; [g] Mannino DM, et al. *MMWR Surveill Summ*. 2002;51(SS-6):1-16.

Expiratory Airflow Limitation Is the Key Determinant of COPD Symptomatology

Normal lung



COPD lung



- Reduced recoil
- Reduced tethering
- Bronchoconstriction
- Increased airway resistance
- Expiratory flow limitation
- Increased air trapping

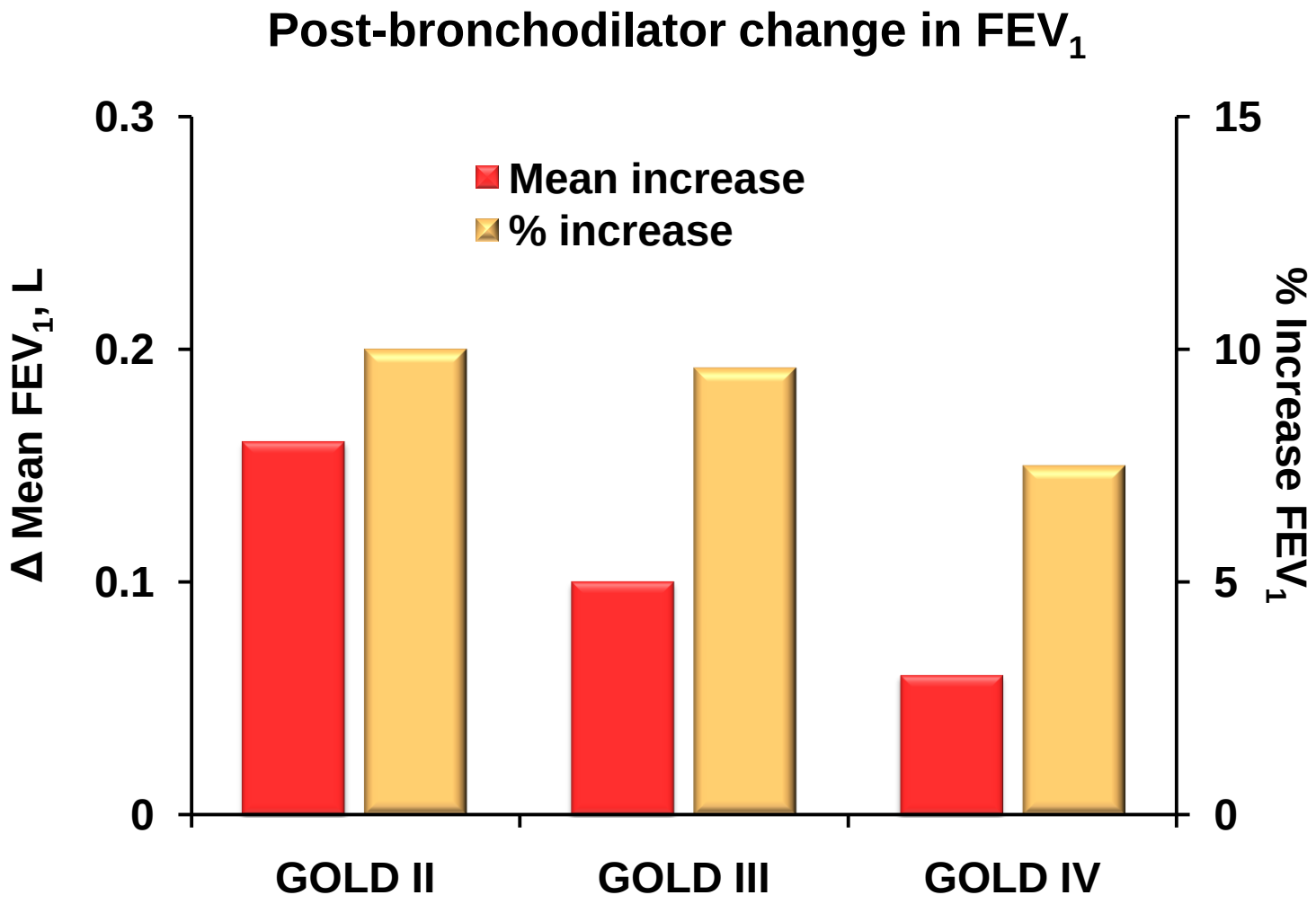
Spirometric Classification of COPD

Post-bronchodilator $FEV_1/FVC < 70\%$ confirms persistent airflow limitation and diagnosis of COPD

	GOLD Post-bronchodilator FEV_1
Mild	GOLD I: $FEV_1 \geq 80\%$ predicted
Moderate	GOLD II: $50\% \leq FEV_1 < 80\%$ predicted
Severe	GOLD III: $30\% \leq FEV_1 < 50\%$ predicted
Very Severe	GOLD IV: $FEV_1 < 30\%$ predicted

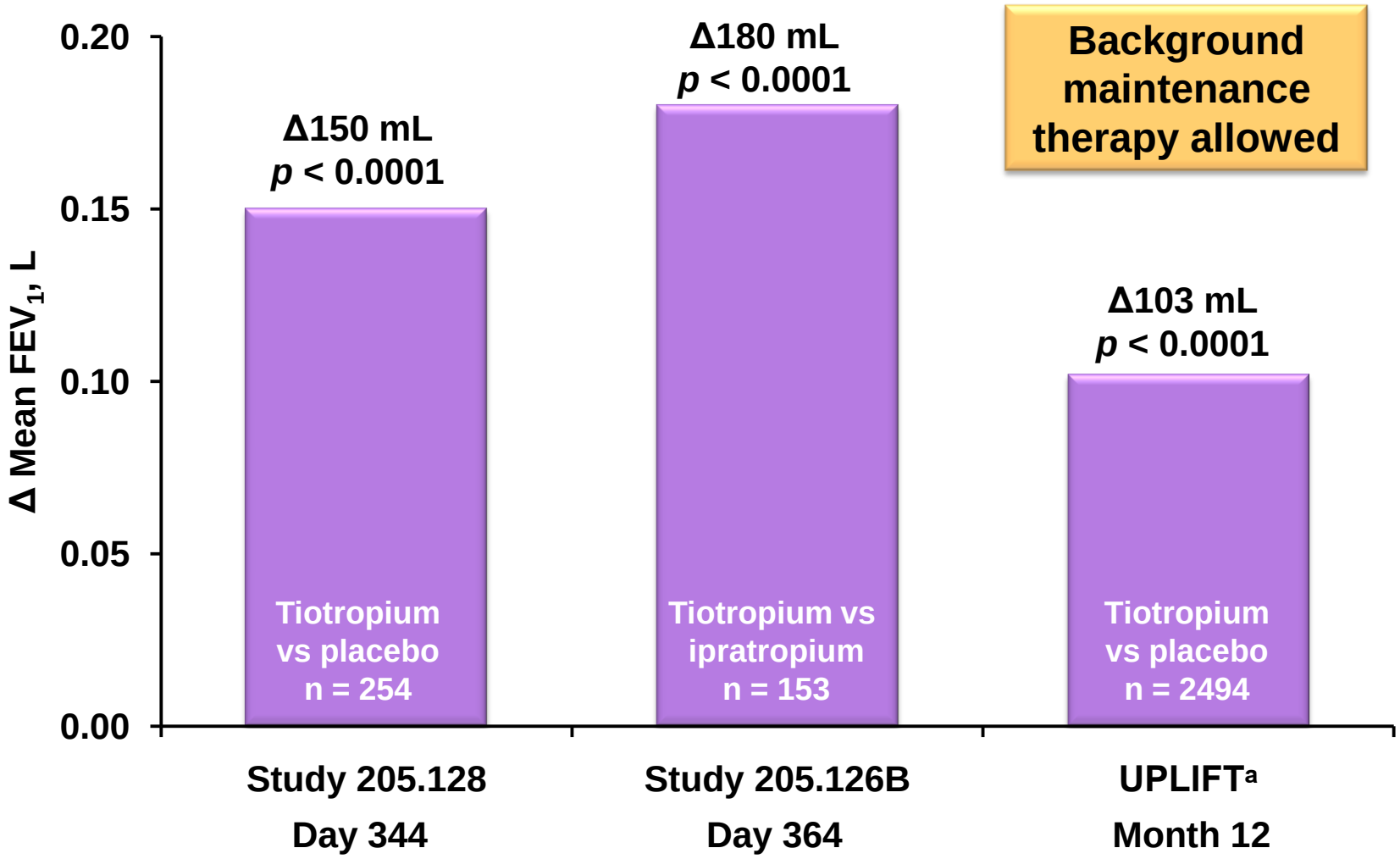
The Global Initiative for Chronic Obstructive Lung Disease, http://www.goldcopd.org/uploads/users/files/GOLD_Pocket_May2512.pdf. Accessed Aug 13, 2012.

All Stages of COPD Respond to Acute Administration of Inhaled Albuterol



Data from Albert P, et al. *Thorax.* 2012;67:701-708.

Greater Amounts of Maintenance Therapy Limit FEV_1 Trough Increases



[a] UPLIFT: 4-year COPD outcome study.

Summary of Medical Need in COPD Patients

- Maintenance bronchodilator therapy is central to meeting treatment goals, which include
  - Improved lung airflow
  - Reduced rescue medication use
  - Reduced symptoms of dyspnea
  - Improved quality of life
  - Improved ability to exercise

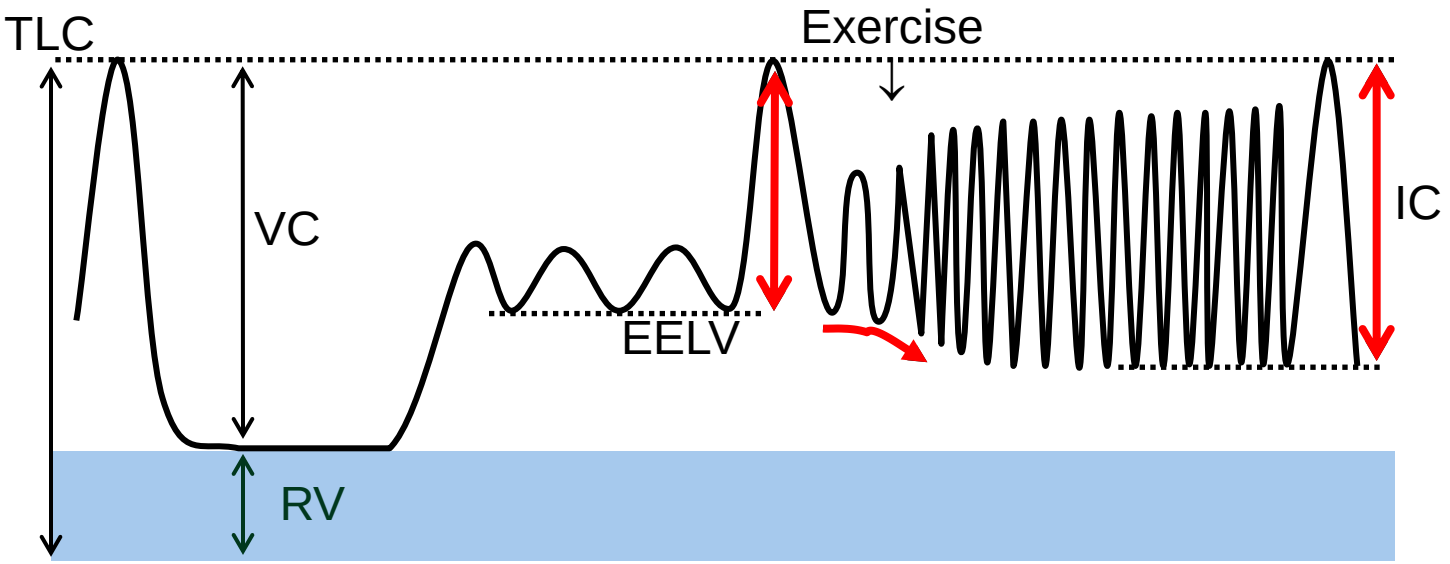
COPD and Exercise

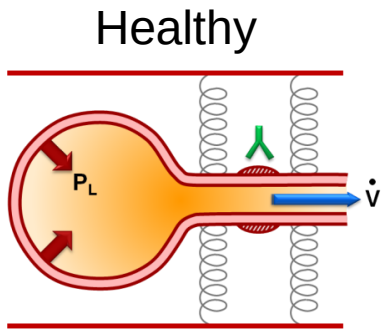
- Patients with even mild COPD demonstrate reduced exercise tolerance[a]
- Dyspnea on exertion is often the chief complaint of COPD patients
- Dynamic hyperinflation is the predominant mechanism of exercise limitation[b]

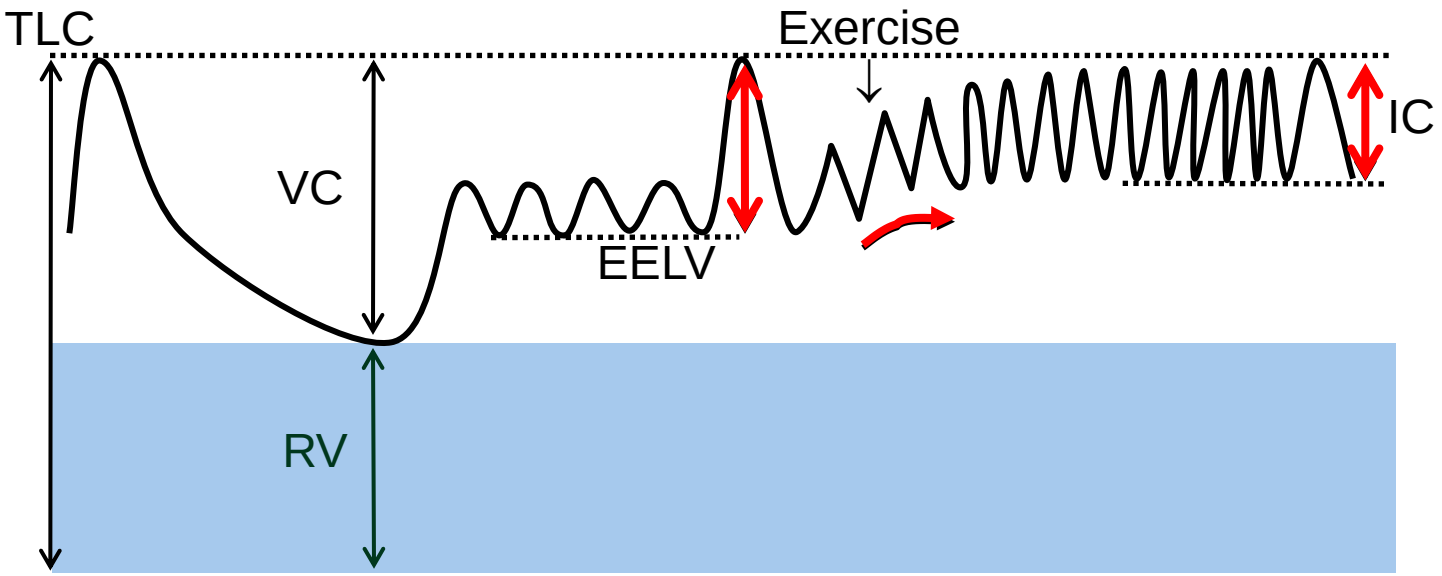
[a] Babb TG, Rodarte JR. *Med Scie Sports Exerc.* 1992; [b] Casaburi R, Porszasz J. *Proc Am Thorac Soc.* 2006.

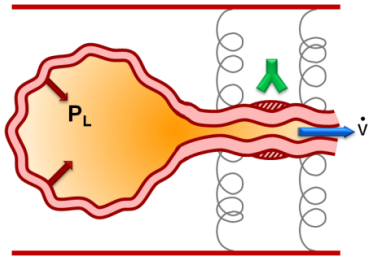
COPD Patients Experience Lung Hyperinflation

Lung Volume Response to Exercise









Assessing Exercise Tolerance—Constant Work Rate Testing

- Pulmonary society statements recommend constant work rate testing to assess exercise response to interventions[a]
  - Determines how long a task can be sustained
- Cycle ergometry allows precise metering of work rate
  - Involves designing a work rate for each individual that can be tolerated for a targeted period of time
- Change in exercise duration is a more sensitive measure of improvement in exercise capacity

[a] ATS/ACCP Statement on Cardiopulmonary Exercise Testing. *AJRCCM*. 2003;167:211-277.
ERS Task Force: Recommendations on the use of exercise testing in clinical practice. *ERJ*. 2007;29:185-209.

Assessing Exercise Tolerance—Constant Work Rate Testing

- Isotime concept: Response to an identical exercise task (same work rate, same duration)
- Cross-over design: Comparing isotime responses before and after an intervention allows determination of the *effort-independent* physiologic benefits of an intervention

Summary of Medical Need in COPD Patients

- Maintenance bronchodilator therapy is central to meeting treatment goals, which include
  - Improved lung airflow
  - Reduced rescue medication use
  - Reduced symptoms of dyspnea
  - Improved quality of life
  - Improved ability to exercise

Olodaterol Clinical Program

Alan Hamilton, PhD

Clinical Program Leader
Boehringer Ingelheim

Boehringer Ingelheim

Outline of Presentation

- Overview of clinical program
- Phase II (COPD and asthma)
- Phase III (COPD)
  - Primary evidence of efficacy (olodaterol 5 µg qd)
- Supportive evidence of efficacy: symptomatic benefit
  - TDI, SGRQ, rescue medication use
- Exercise tolerance

TDI = Transition Dyspnea Index; SGRQ = St. George's Respiratory Questionnaire.

Terminology

- FEV_1: primary efficacy variable
  - FEV_1 AUC_{0-3}
    - Area under the FEV_1-time curve from 0 to 3 hr post-dose
    - Divided by time (3 hr): weighted average FEV_1 (L) over 3-hr post-dose period
  - Trough FEV_1
    - FEV_1 at end of 24-hr dosing interval, prior to next dose
- Baseline FEV_1
  - Pre-treatment value
  - Average of –1 hr and –10 min prior to first dose
- FEV_1 Response (FEV_1 AUC_{0-3} response, trough FEV_1 response)
  - Change from baseline

FEV_1 = Forced Expiratory Volume in 1 second.

Olodaterol Clinical Program COPD/Asthma

Dose-ranging (once daily)	Once daily vs twice daily	Phase III		
		Pivotal	24-hr profile	Exercise
COPD				
Study 3 Study 5 Study 22[a]	Study 26	Studies 11/12 Studies 13/14	Studies 24/25 Studies 39/40	Studies 37/38
Asthma				
Study 4 Study 6 Study 27	Study 29	No Phase III program		

[a] **Japanese COPD patients, for purposes of registration in Japan.**

Outline of Presentation

- Overview of clinical program
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  - Primary evidence of efficacy (olodaterol 5 µg qd)
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  - TDI, SGRQ, rescue medication use
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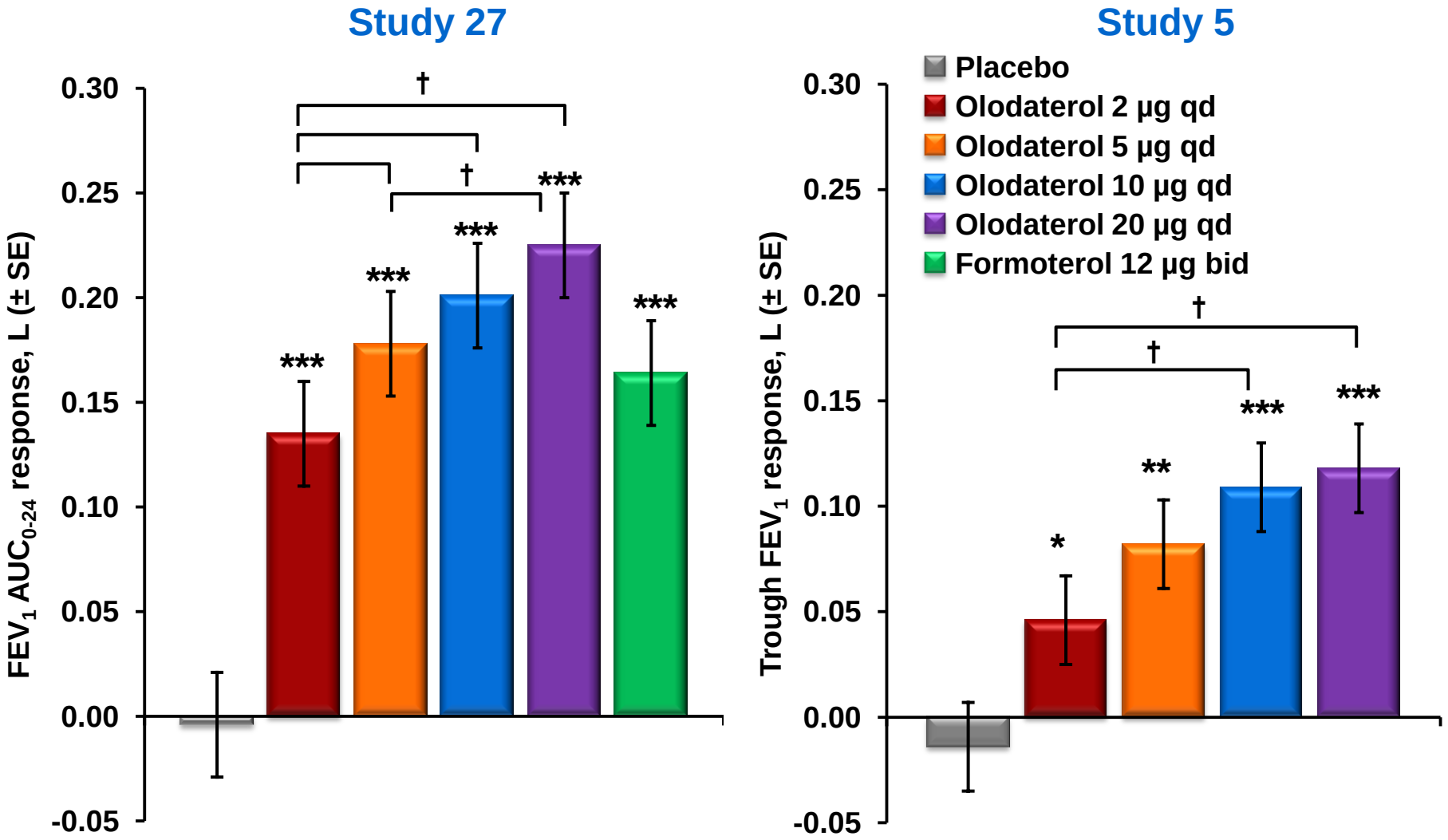
Adjusted Mean FEV_1 Response After 4 Weeks in Asthma (Study 27) and COPD (Study 5)



Difference from placebo: *$p < 0.05$; ** $p < 0.001$; *** $p < 0.0001$; difference between treatments: † $p < 0.05$.
Analysis with imputation (FAS).

Outline of Presentation

- Overview of clinical program
- Phase II (COPD and asthma)
- Phase III: primary evidence of efficacy (olodaterol 5 µg qd)
  - Pivotal studies: study design
  - Efficacy results
    - FEV_1 $AUC_{0\text{-}3}$, trough FEV_1
    - 24-hr bronchodilating profile
    - 5 µg once daily vs 10 µg once daily
  - Effect size: trial design considerations
- Supportive evidence of efficacy: symptomatic benefit
  - TDI, SGRQ, rescue medication use
- Exercise tolerance

Phase III Clinical Program (COPD)

	Olodaterol 5 µg once daily, 10 µg once daily				
	Long-term efficacy, safety		24-hr lung function		Exercise
Study	11/12	13/14	24/25	39/40	37/38
Design	R, DB (DD), PC parallel group		R, DB, DD, PC crossover		R, DB, PC crossover
Duration	48 weeks		6 weeks		6 weeks
AC	—	Formoterol	Formoterol	Tiotropium HH	—
1° variable	• FEV_1 AUC_{0-3} • Trough FEV_1	• FEV_1 AUC_{0-3} • Trough FEV_1 • TDI focal score	• FEV_1 AUC_{0-12} • FEV_1 AUC_{12-24}	• FEV_1 AUC_{0-12} • FEV_1 AUC_{12-24}	• Exercise ET
Key 2° variable		• SGRQ total score	• FEV_1 AUC_{0-24}	• FEV_1 AUC_{0-24}	• IC • Borg BD

Agreement (End-of-Phase II Meeting)
Totality of evidence from Phase III program used to evaluate efficacy of olodaterol (ie, not only 11 and 12)

AC = active comparator; BD = breathing discomfort; ET = endurance time; IC = inspiratory capacity; R, DB (DD), PC = randomized, double-blind (double dummy), placebo-controlled.

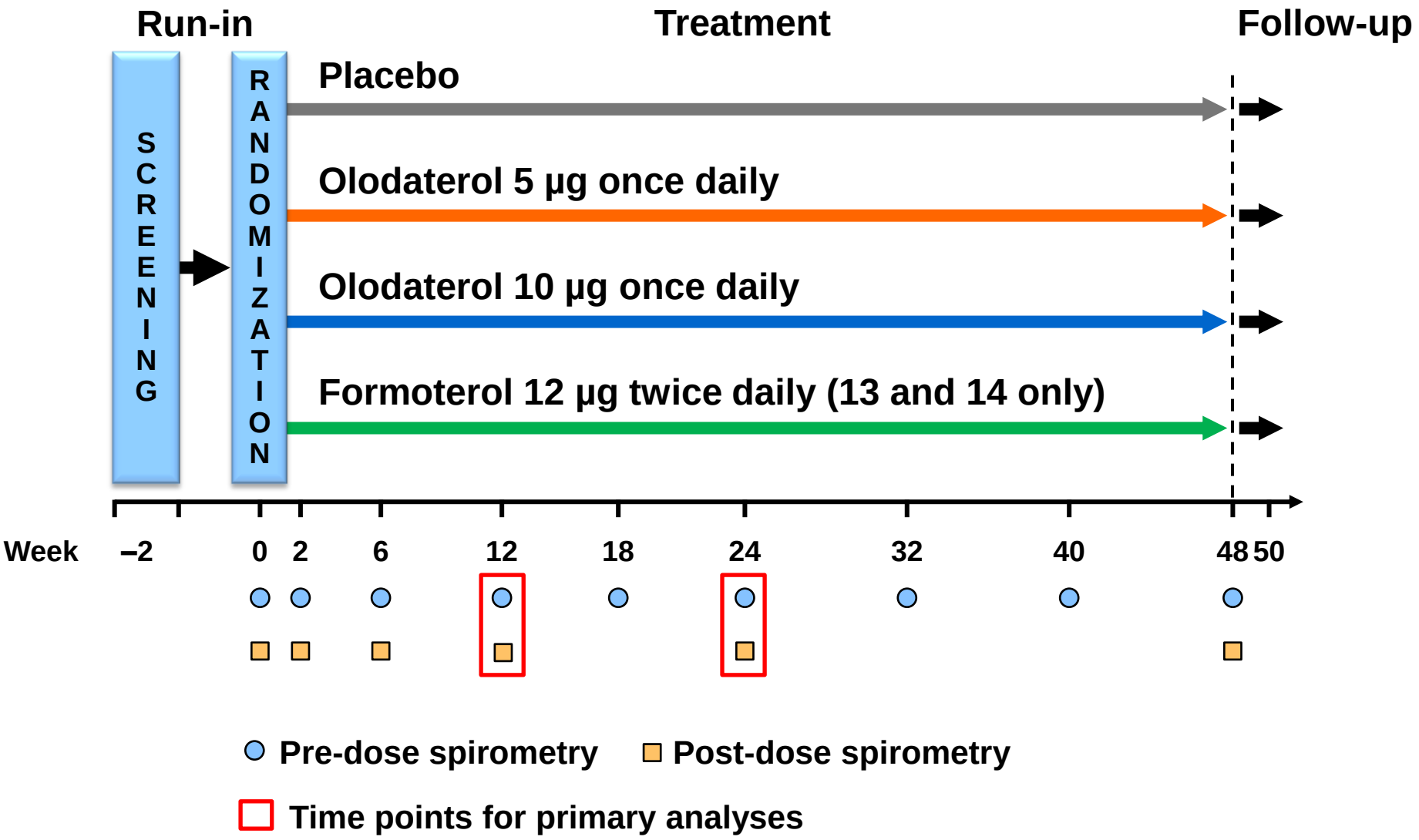
Long-term Efficacy (FEV_1)

Replicate studies 11 and 12 (US requirements)

Replicate studies 13 and 14 (EU requirements)

Study Design (Lung Function)

Studies 11 and 12, Studies 13 and 14



Patient Population

- Diagnosis of COPD
  - Male or female, ≥ 40 yr of age
- Current/ex-smoker
  - Smoking history ≥ 10 pack-years
- Post-bronchodilator spirometry
  - FEV_1 < 80% predicted (GOLD II/III/IV)
  - FEV_1/FVC < 70%

- *Asthma patients specifically excluded*

Concomitant Medications

- Bronchodilators
  - **SAMA: Allowed[a]**
  - **LAMA: Allowed[a] [stratified]**
  - LABA: Withdrawn prior to study entry (switch to ipratropium allowed)
  - SABA: Rescue medication (albuterol)
- Anti-inflammatories
  - Oral steroids: Allowed (low dose)[a]
  - Inhaled steroids: Allowed[a]
  - Xanthines (theophylline): Allowed[a]

[a] **If used as maintenance therapy at study enrollment.**

Demographics

	Study			
	11	12	13	14
Patients, N	624	642	904	934
Male, %	73.2	71.0	78.1	81.2
Age, mean (yr)	64.9	64.6	63.8	64.1
Race, %				
White	62.7	63.7	70.9	66.5
Black/African American	1.9	3.0	0.7	0.2
Asian	34.1	33.0	28.2	33.2
Other	1.3	0.3	0.2	0.1
Smoking history				
Ex-smoker, %	61.4	56.2	65.0	67.0
Smoker, %	38.6	43.8	35.0	33.0
Pack-years, mean	48.8	50.3	45.1	42.5

Concomitant Pulmonary Medications
Studies 11-14

Medication during treatment

Patients, N	3,104
Muscarinic antagonist,[a] n (%)	1,453 (46.8)
Anti-inflammatory,[b] n (%)	1,627 (52.4)
Muscarinic antagonist + anti-inflammatory,[b] n (%)	888 (28.6)
Muscarinic antagonist + ICS + xanthines, n (%)	163 (5.3)
LABA prior to study entry, N (%)	1,140 (36.7)
– With muscarinic antagonist, n	628
– Without muscarinic antagonist, n	512

[a] SAMA/LAMA; [b] ICS/xanthine.

Spirometry at Screening

	Study			
	11	12	13	14
Patients, N	624	642	904	934
Pre-bronchodilator				
Mean FEV_1, L	1.165	1.194	1.247	1.252
Post-bronchodilator				
Mean FEV_1, L (% predicted)	1.338 (48.8)	1.356 (48.9)	1.408 (51.2)	1.402 (51.5)
Mean change from pre-BD, L (%)	0.172 (16.6)	0.162 (15.6)	0.161 (14.9)	0.150 (13.6)
FEV_1/FVC, %	45.3	45.7	46.0	47.4
GOLD, %				
Stage I	0	0.3	0.1	0.5
Stage II	46.0	47.2	53.7	52.1
Stage III	42.0	39.4	38.5	38.9
Stage IV	12.0	13.1	7.7	8.5

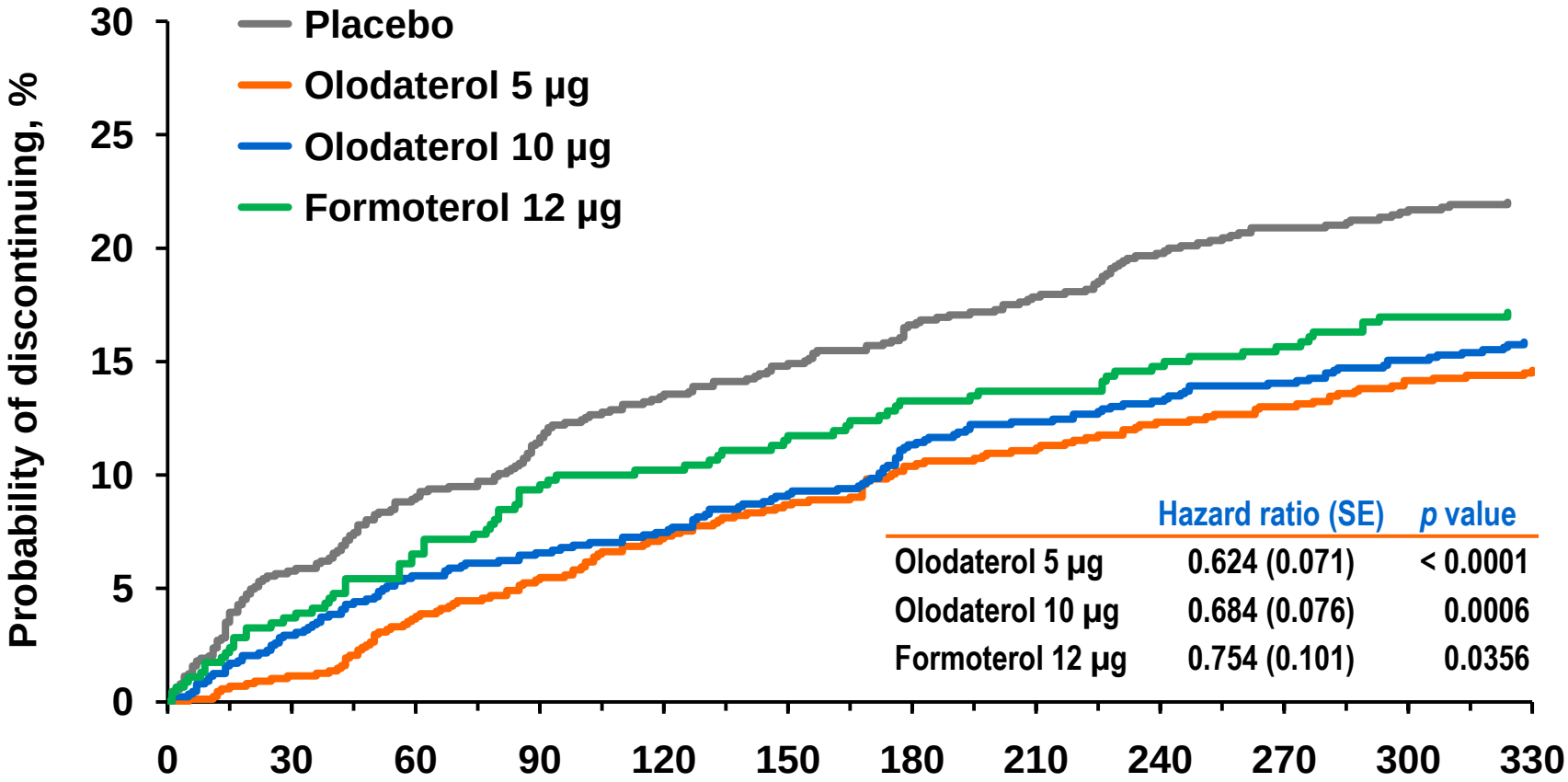
Patient Disposition

	Study			
	11	12	13	14
Enrolled, n	859	892	1212	1257
Treated, n	624	642	904	934
FAS, n	620	637	885	928
Completed study, %	80.8	84.3	80.6	82.4
Prematurely discontinued, %				
Adverse event	8.7	7.8	7.6	7.2
Lack of efficacy	2.9	2.7	1.7	1.5
Consent withdrawn	4.8	2.5	6.0	4.8
Completed 1° endpoint, %	91.5	93.6	86.7	89.0

Denominator for percentage is the number of treated patients.

Probability of Discontinuation

Studies 11-14 (Pooled Dataset)



Patients at risk

Placebo	885	834	805	782	765	753	738	727	710	700	693
Olo 5 µg	876	866	843	828	812	800	785	778	768	762	751
Olo 10 µg	883	857	834	825	817	802	783	774	766	759	749
Form 12 µg	460	443	430	416	413	406	399	397	392	388	382

Efficacy Results

Olodaterol 5 µg once daily vs placebo

- Studies 11 and 12
- Studies 13 and 14

Lung Function Measurements

- Spirometry
  - **FEV_1 AUC_{0-3} response (primary endpoint)**
    - Post-dose: 5, 15, 30 min; 1, 2, 3 hr
    - Peak bronchodilation
  - **Trough FEV_1 response (primary endpoint)**
    - Pre-dose: 1 hr, 10 min
    - Bronchodilation at end of dosing interval (dose taken day before clinic visit)
- Time point of primary analysis
  - Studies 11 and 12: 12 weeks (US requirement)
  - Studies 13 and 14: 24 weeks (EU requirement)

Hierarchical Testing Strategy
Protection Against Type I Error

Studies 11, 12, 13, 14: Identical testing strategy for lung function

1. Olodaterol 10 µg vs placebo
   - ↳ FEV_1 AUC_{0-3} response (1° endpoint)
     - ↳ Trough FEV_1 response (1° endpoint)
2. Olodaterol 5 µg vs placebo
   - ↳ FEV_1 AUC_{0-3} response (1° endpoint)
     - ↳ Trough FEV_1 response (1° endpoint)

Studies 13, 14: Additional testing strategy for TDI[a], SGRQ[a]

3. TDI focal score (1° endpoint)
   - ↳ Olodaterol 10 µg vs placebo
     - ↳ Olodaterol 5 µg vs placebo
4. SGRQ total score (key 2° endpoint)
   - ↳ Olodaterol 10 µg vs placebo
     - ↳ Olodaterol 5 µg vs placebo

[a] **Combined dataset.**

Primary Analysis—Lung Function

- Primary population (Full Analysis Set [FAS]; ITT principle)
  - Baseline data
  - ≥ 1 dose of study drug
  - ≥ 1 on-treatment measurement[a]
- Mixed-effects model for repeated measures (MMRM)
  - Categorical: Treatment, tiotropium use stratum, test day, treatment by test day interaction
  - Continuous: Baseline, baseline by test day interaction
  - All interactions with stratum were removed

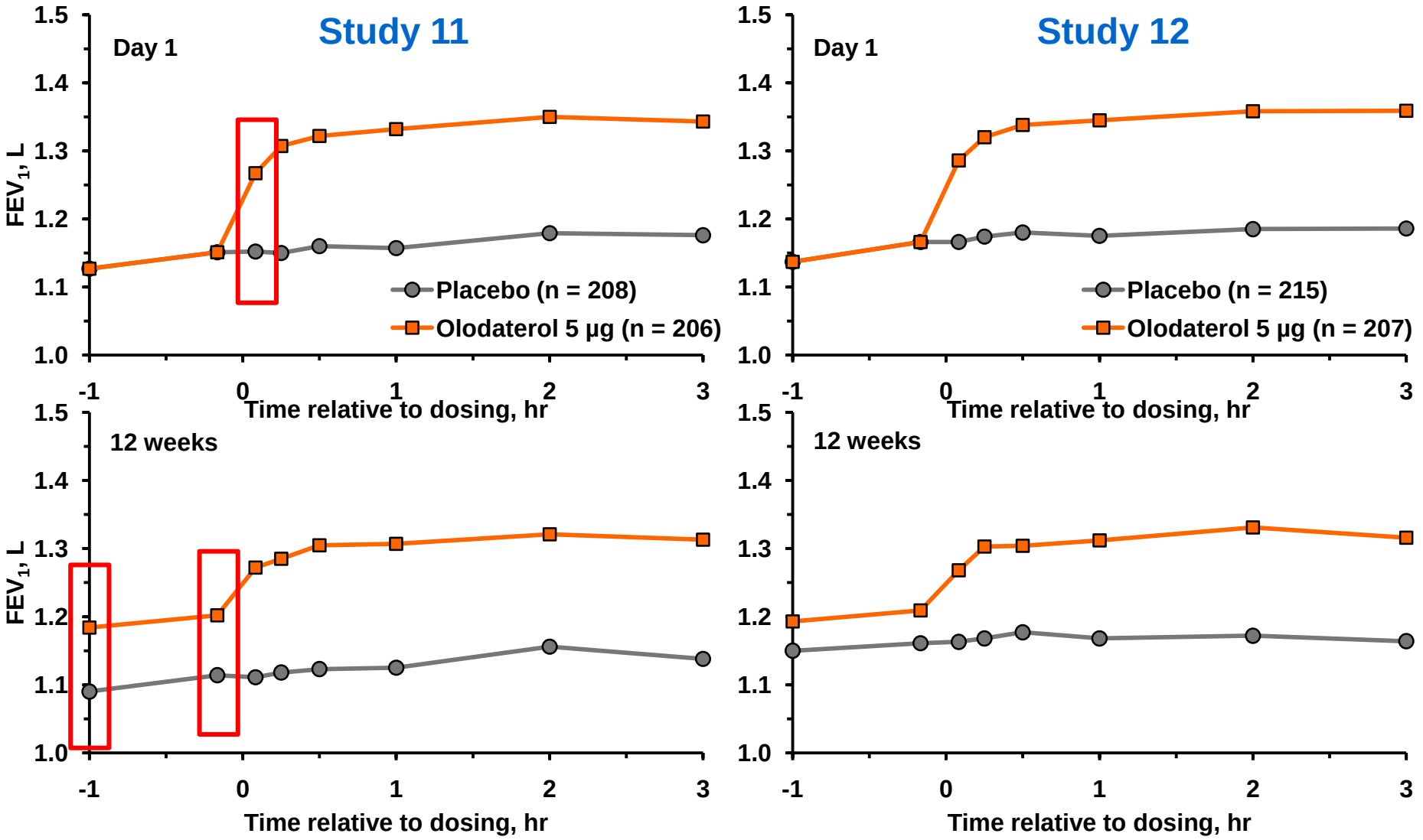
[a] For at least 1 primary endpoint on or before primary endpoint visit

Lung Function Improvements
Evaluation of Clinical Relevance

- Novel clinical program
  - GOLD II-IV
  - Usual care background therapy

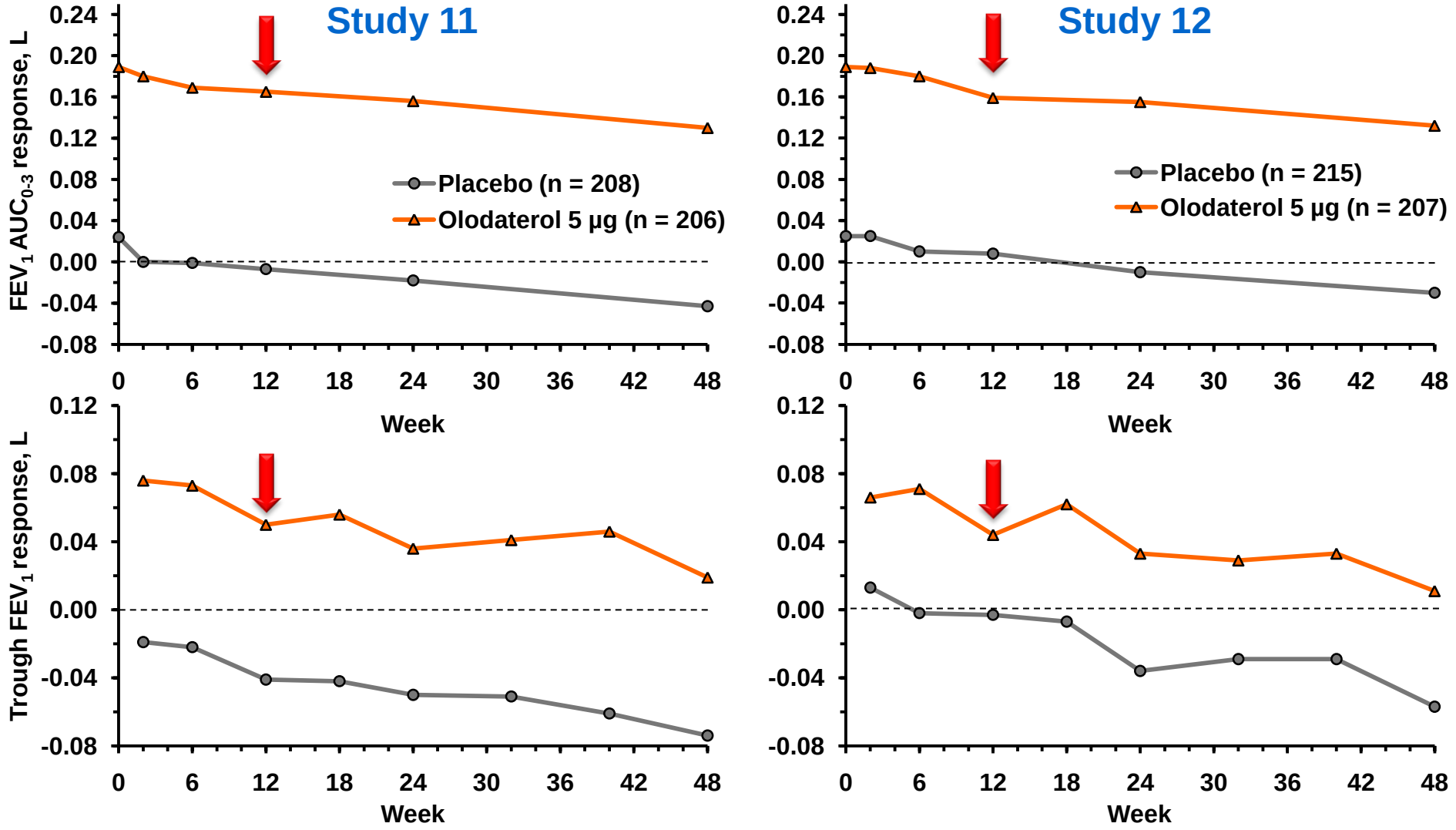
- Clinical relevance of lung function improvements:
  - Characterization of SABA responsiveness
  - Active comparators of known therapeutic benefit
  - Symptomatic benefit
  - Lung function efficacy under traditional trial conditions

Adjusted Mean FEV_1
Studies 11 and 12



Common baseline mean (SE): Study 11, 1.139 (0.019); Study 12, 1.151 (0.020).
Analysis with imputation (FAS); $p < 0.05$ vs placebo at all time points.

Adjusted Mean FEV_1 AUC_{0-3} and Trough FEV_1 Response Over 48 Weeks



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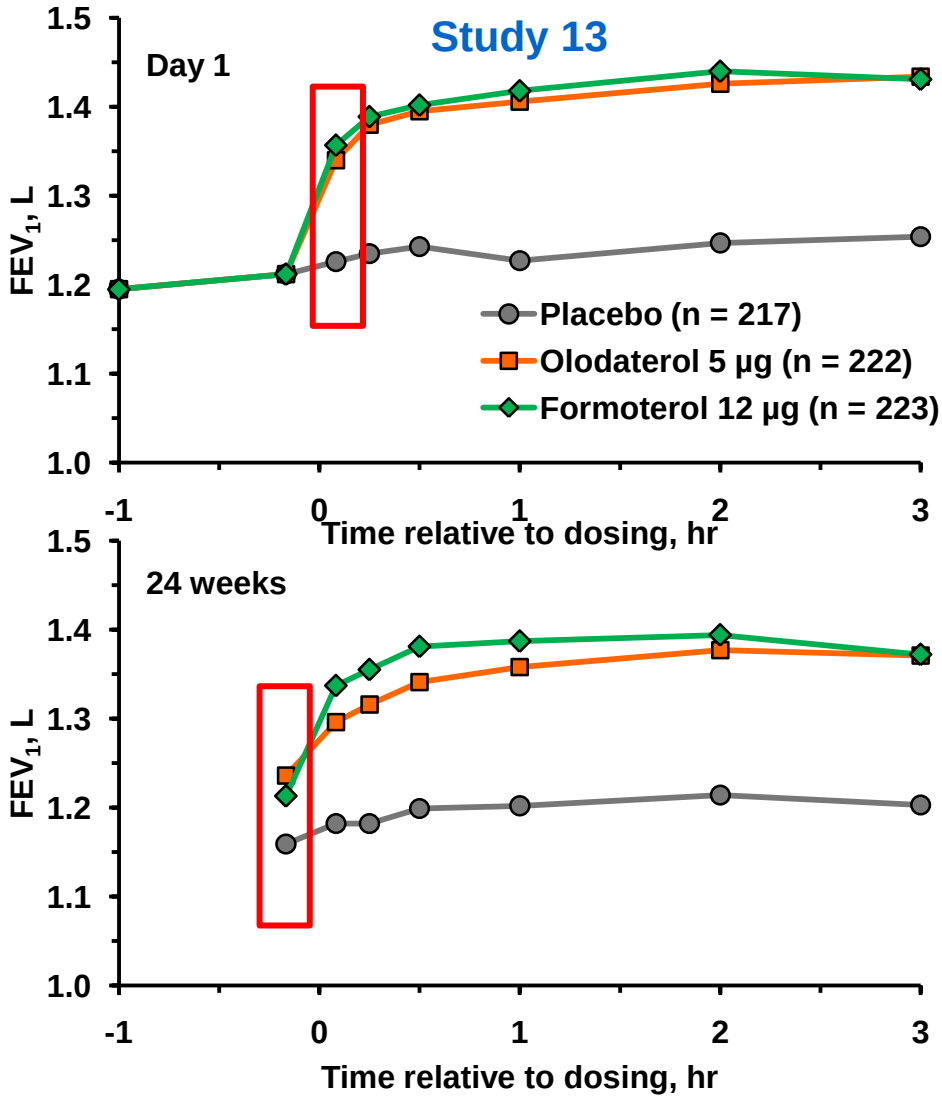
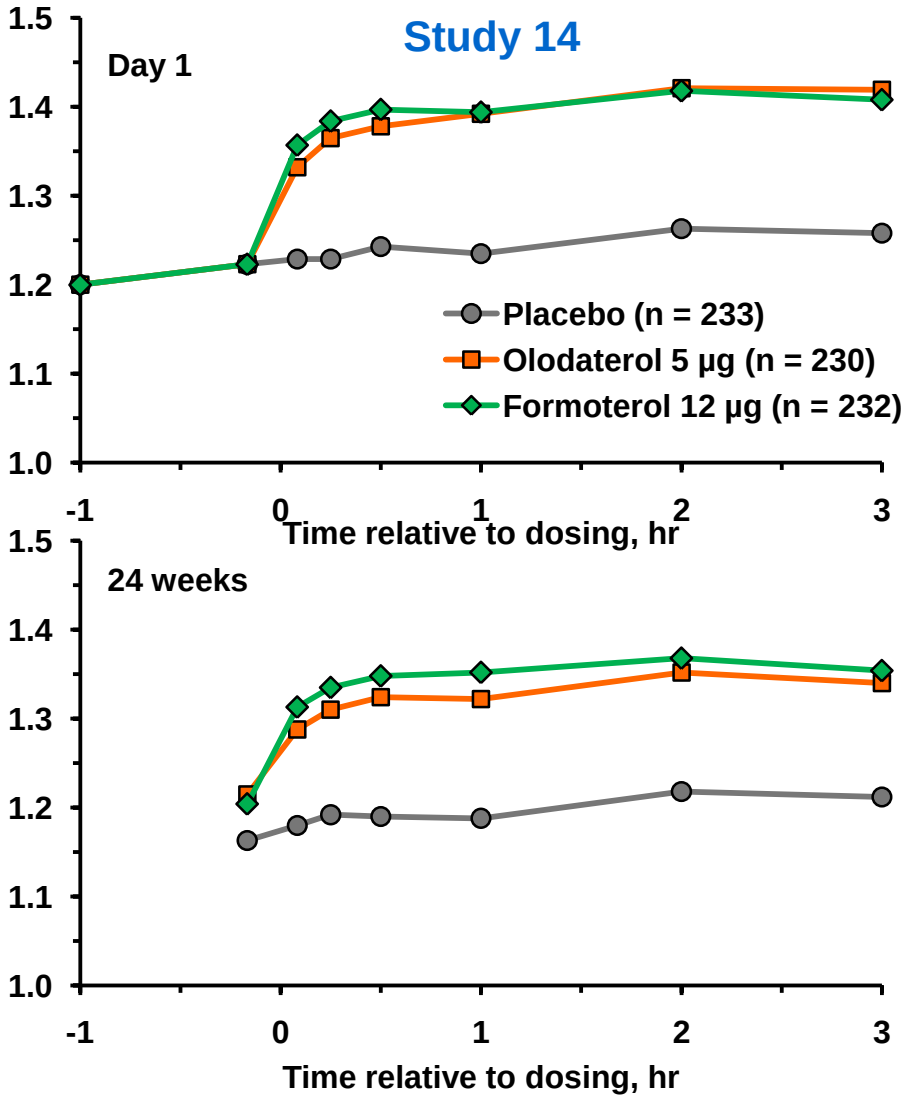
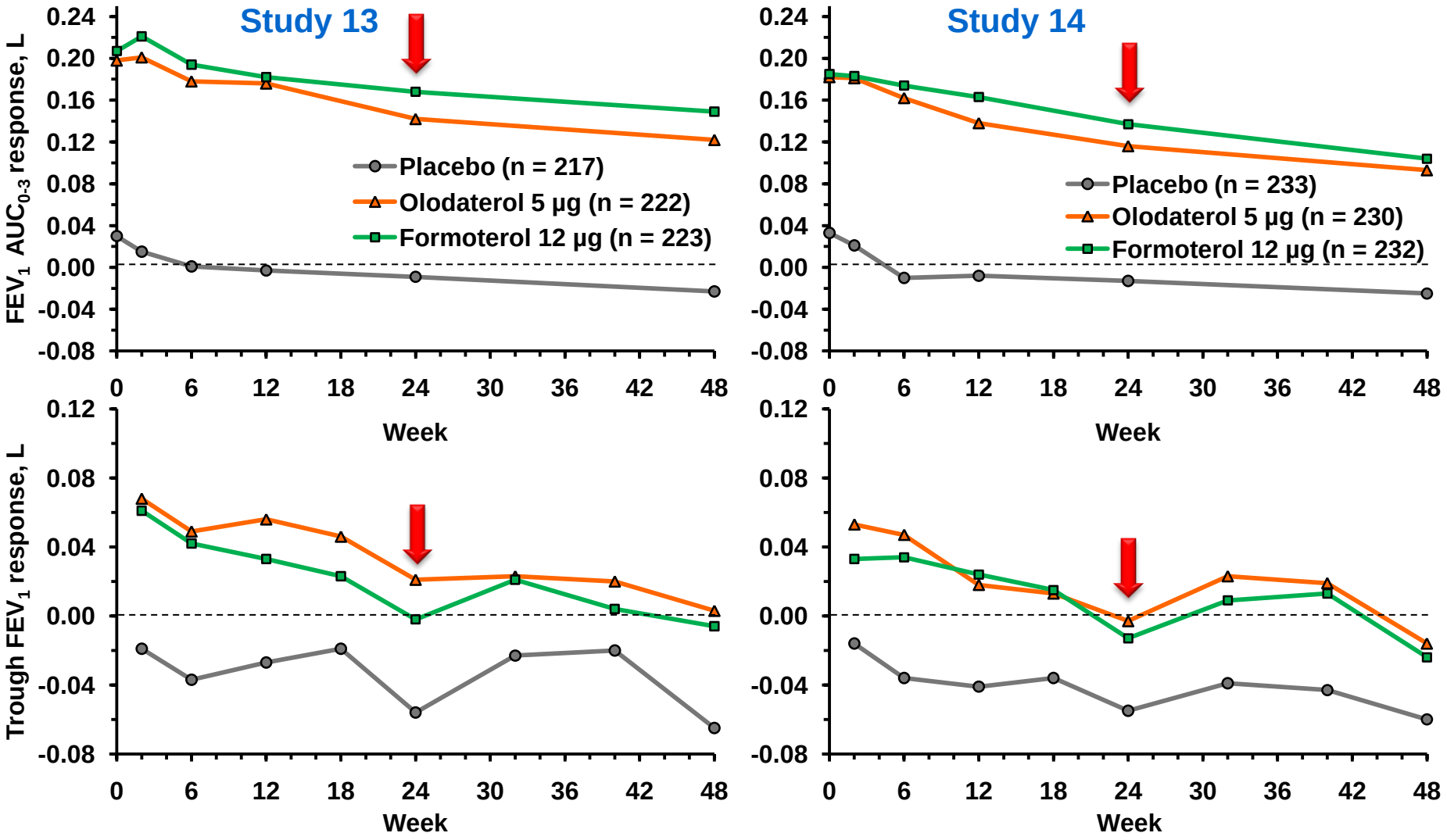
Adjusted Mean FEV_1
Studies 13 and 14





Common baseline mean (SE): Study 13, 1.204 (0.016); Study 14, 1.211 (0.015).
Analysis with imputation (FAS); $p < 0.05$ vs placebo at all time points.

Adjusted Mean FEV_1 AUC_{0-3} and Trough FEV_1 Response Over 48 Weeks



Common baseline mean (SE): Study 13, 1.204 (0.016); Study 14, 1.211 (0.015).
Analysis with imputation (FAS); $p < 0.05$ vs placebo at all time points.

Pivotal Studies
Primary Endpoints (Weighting by Stratum Size)

- **Olodaterol vs placebo**
  - **Studies 11 and 12[a] (12 weeks)**
    - FEV_1 AUC_{0-3} response: Statistically significant
    - Trough FEV_1 response: Statistically significant
  - **Studies 13 and 14 (24 weeks)**
    - FEV_1 AUC_{0-3} response: Statistically significant
    - Trough FEV_1 response: Statistically significant

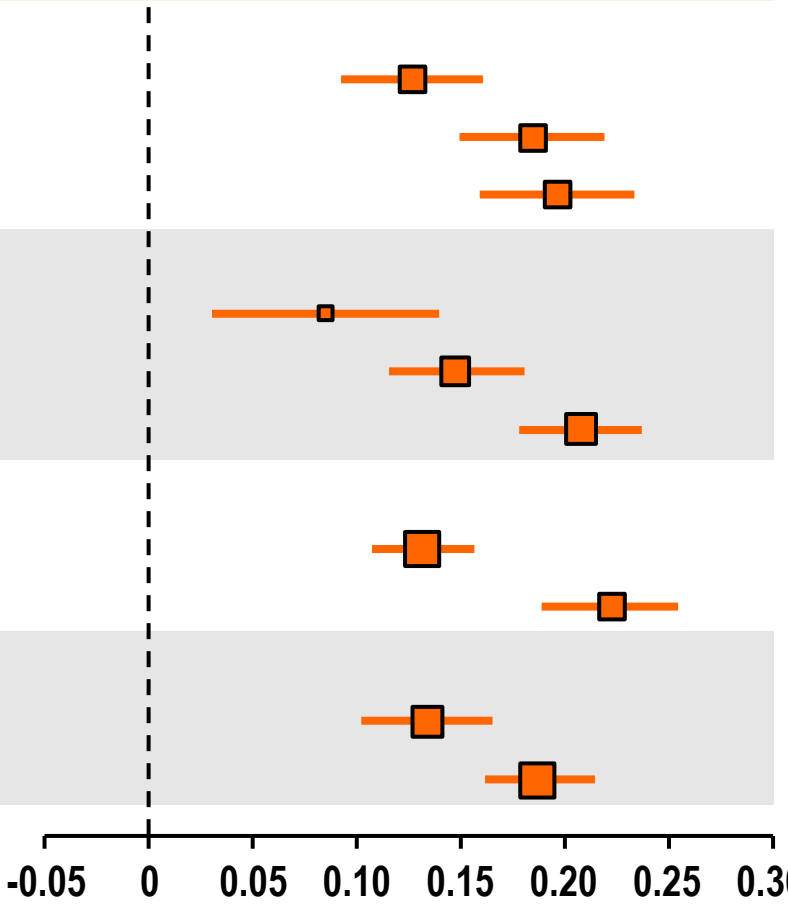
[a] According to original pre-specified analysis, olodaterol vs placebo not significant.

Efficacy in Subgroups

FEV_1 AUC_{0-3} Response by Baseline Spirometry

Studies 11 and 12 Combined Dataset

Subgroup	Placebo N	Placebo Mean	Olo 5 µg N	Olo 5 µg Mean
Pre-bronchodilator FEV_1				
< 35%	146	–0.006	146	0.120
35% - < 50%	137	0.001	149	0.185
≥ 50%	140	0.001	118	0.197
Post-bronchodilator FEV_1				
GOLD IV: < 30%	62	–0.028	51	0.057
GOLD III: 30 - < 50%	154	–0.014	168	0.134
GOLD II: 50 - < 80%	206	0.014	194	0.221
SABA reversibility (> 12%, 0.2 L)				
No	279	–0.008	254	0.124
Yes	144	0.010	159	0.232
SABA reversibility (> 12%)				
No	191	–0.012	162	0.122
Yes	232	0.007	251	0.194



FEV_1 AUC_{0-3} and Trough FEV_1 Response
Influence of Demographic Factors

- **Race (Asian/White)**
  - Lower response in Asians (lower baseline FEV_1, lower responsiveness)
- **Xanthine use**
  - Higher response in patients not using xanthines (small sample size; wide confidence intervals)
- **SAMA use**
  - Higher response in patients not using SAMAs
- **Other factors had similar responses between subgroups**
  - *Tiotropium use*
  - Sex
  - Age
  - Smoking status
  - ICS use
  - LABA use (before study entry)
  - Beta-blockers

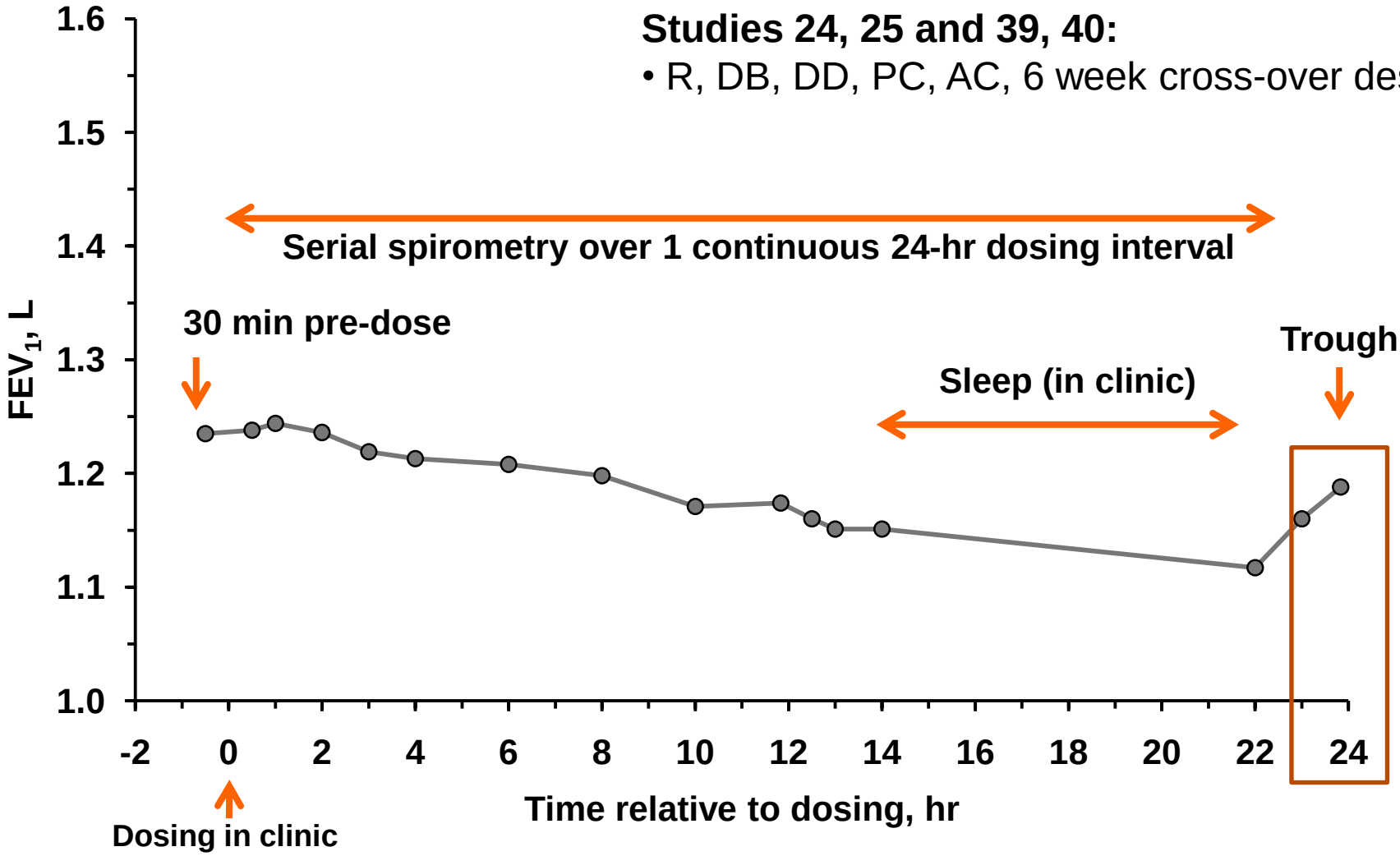
24-hr Bronchodilating Profile

Studies 24, 25

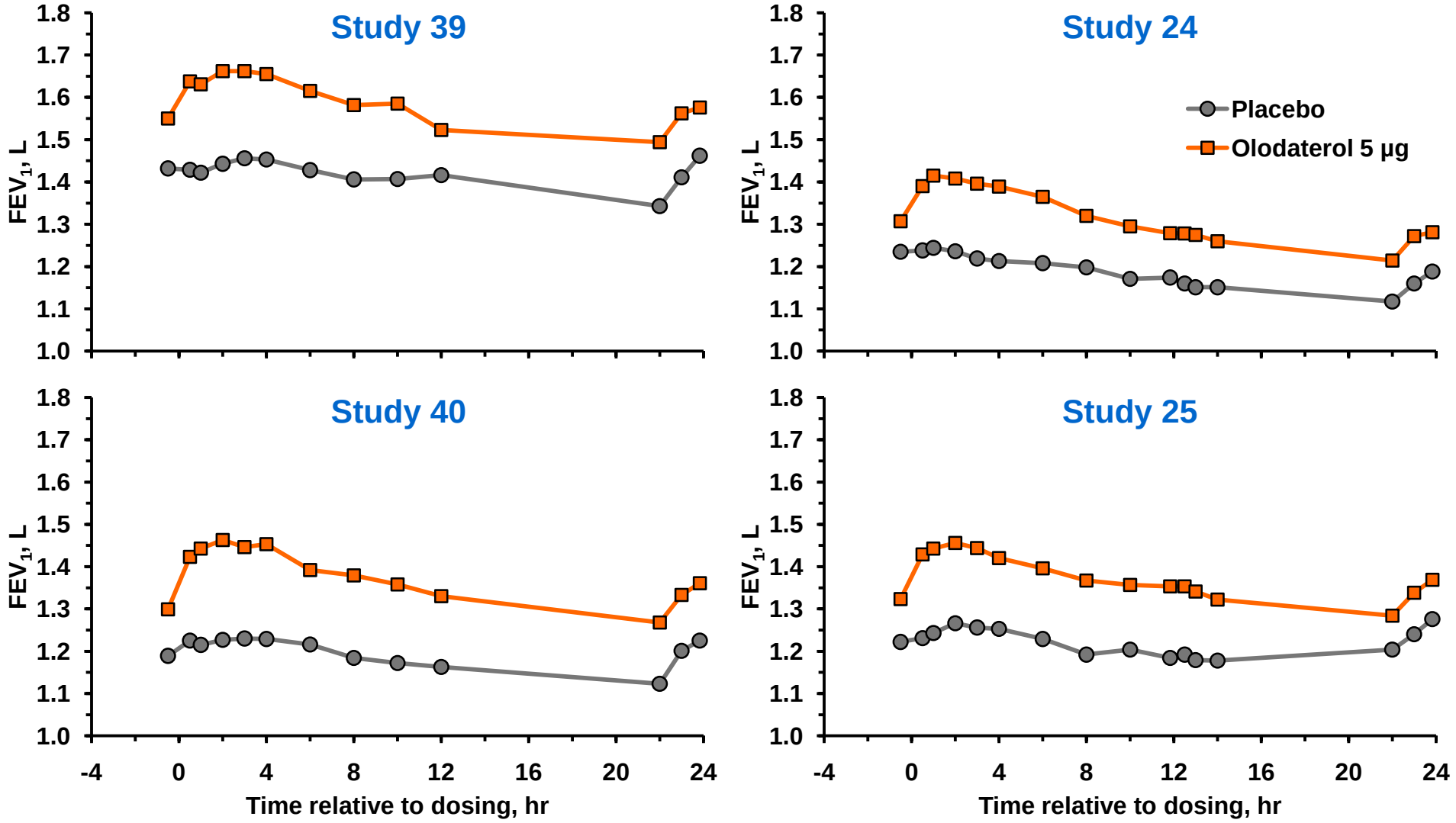
Studies 39, 40

24-hr Lung Function Studies

Rigorous Evaluation of Bronchodilating Profile

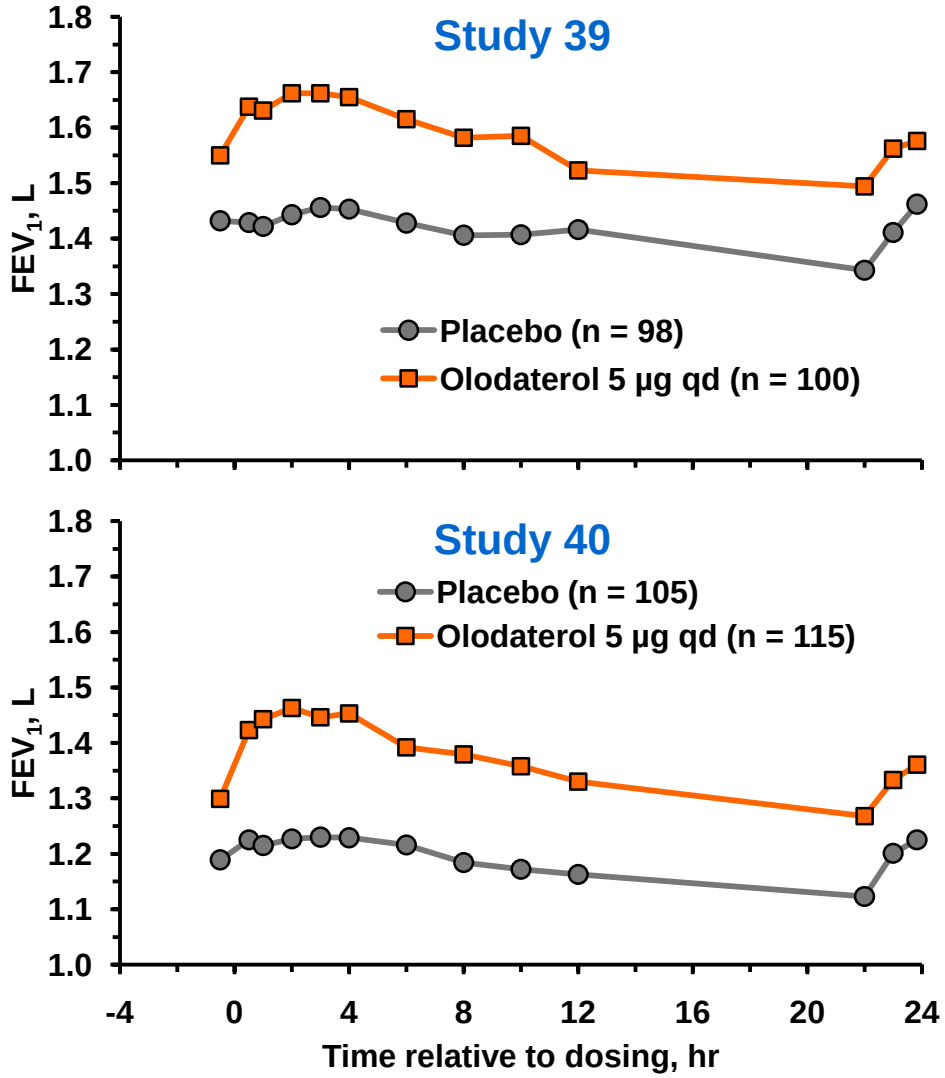


Adjusted Mean FEV_1 Over 24 hr After 6 Weeks



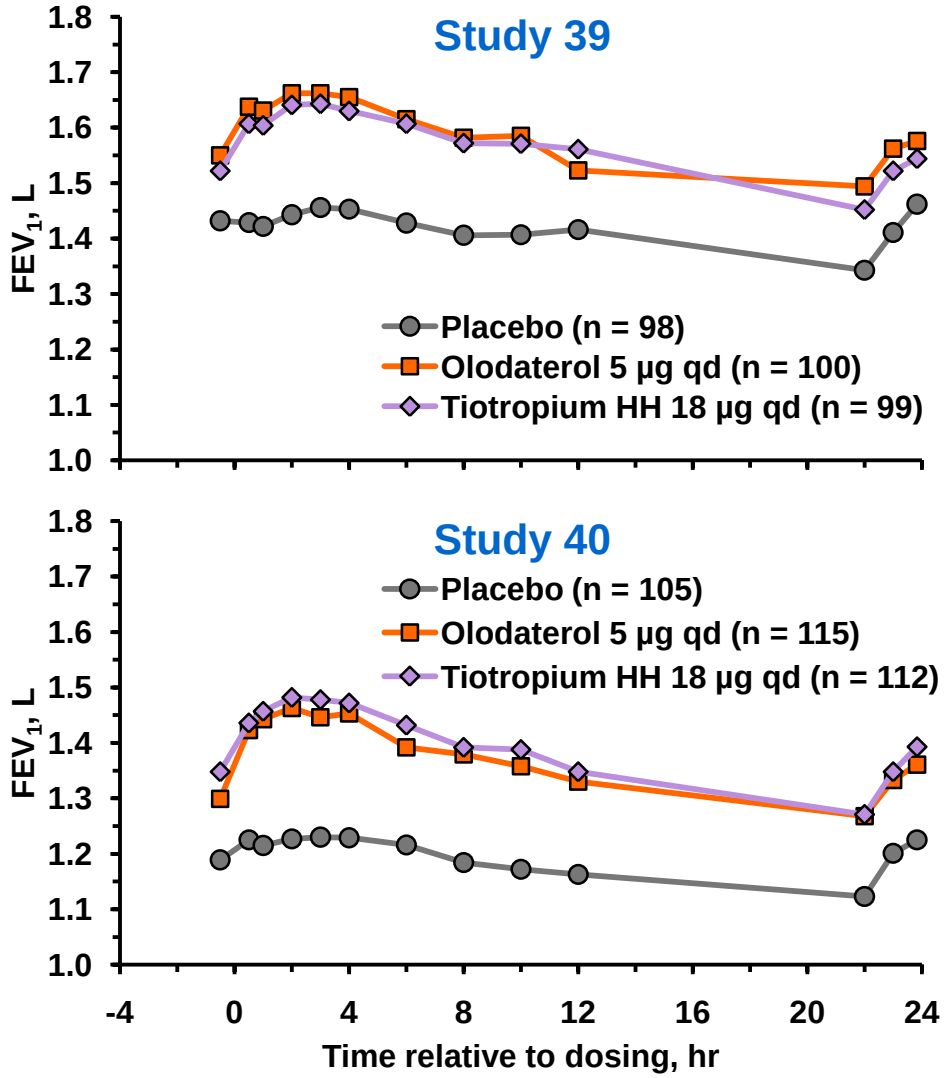
Common baseline mean: Study 24, 1.244; Study 25, 1.249; Study 39, 1.472; Study 40, 1.200.
Analysis with imputation (FAS).

Adjusted Mean FEV_1 Over 24 hr After 6 Weeks



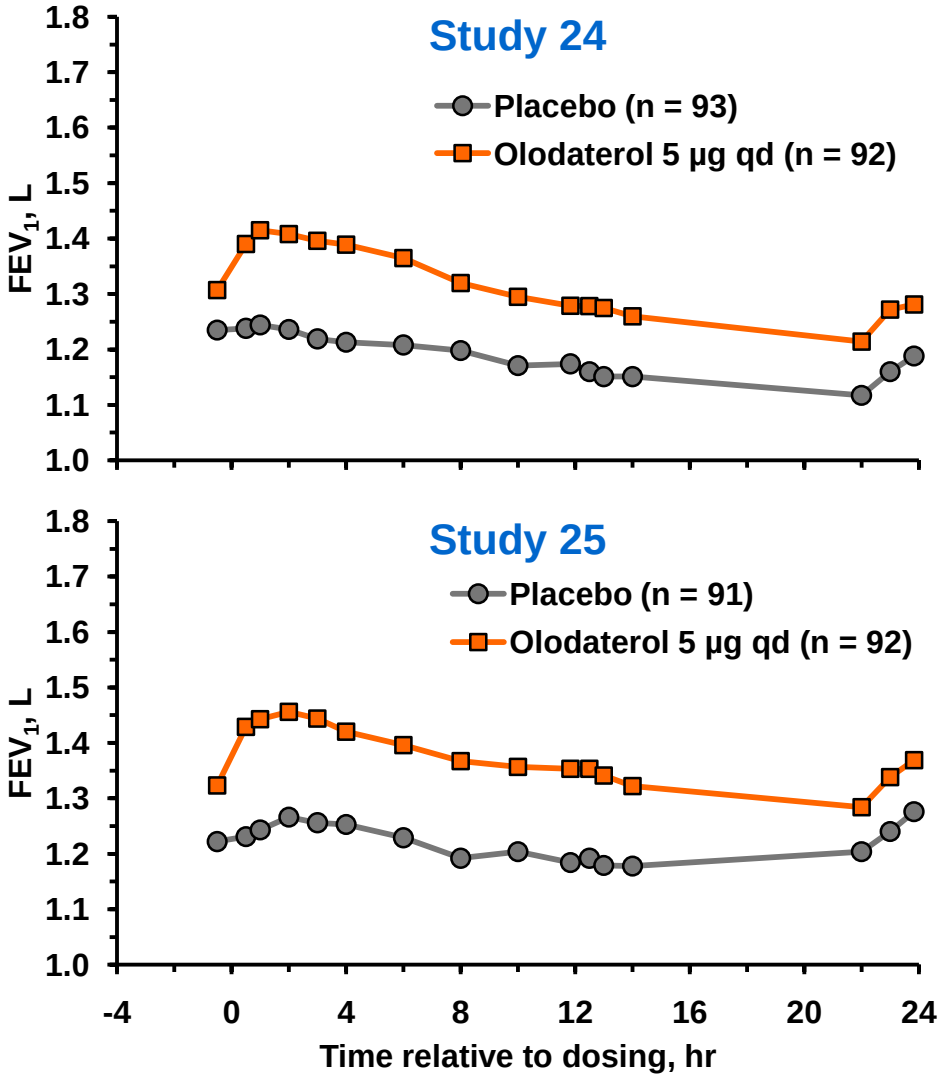
Common baseline mean: Study 24, 1.244; Study 25, 1.249; Study 39, 1.472; Study 40, 1.200.
Analysis with imputation (FAS).

Adjusted Mean FEV_1 Over 24 hr After 6 Weeks



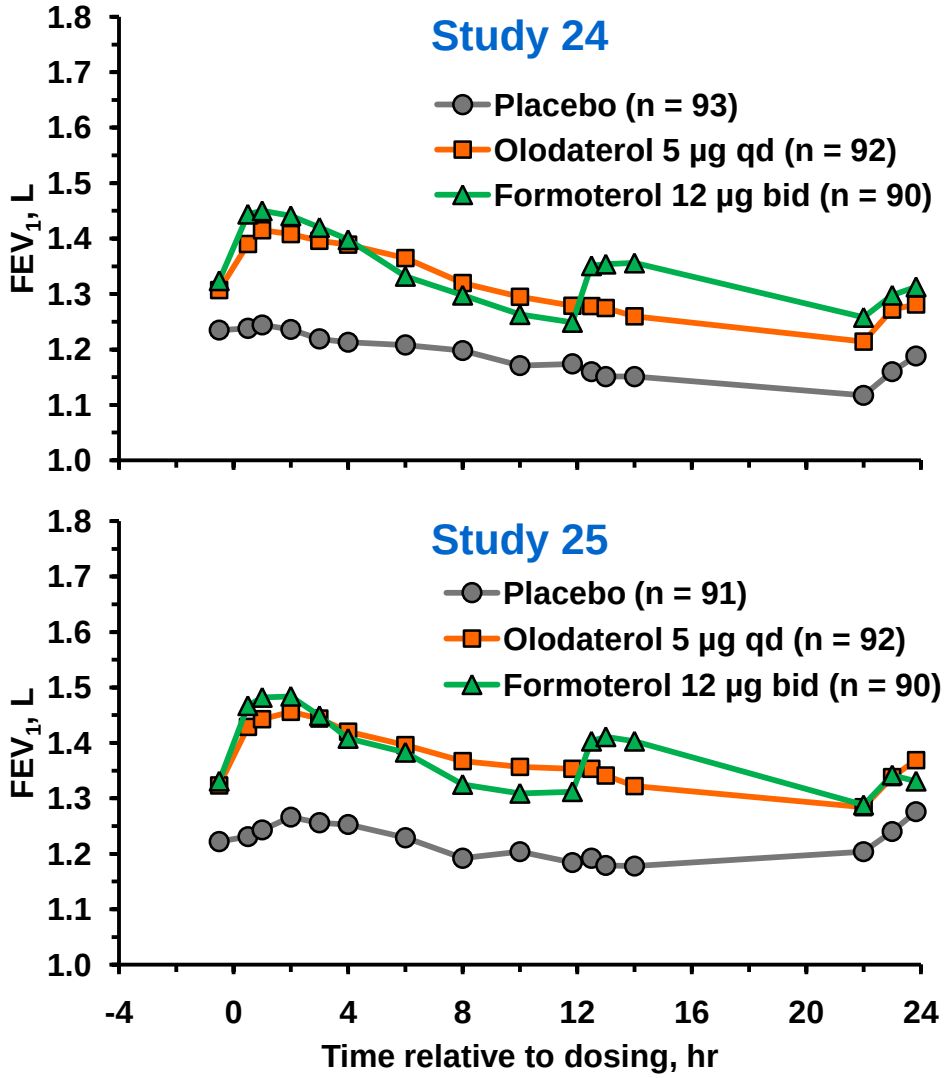
Common baseline mean: Study 24, 1.244; Study 25, 1.249; Study 39, 1.472; Study 40, 1.200.
Analysis with imputation (FAS).

Adjusted Mean FEV_1 Over 24 hr After 6 Weeks



Common baseline mean: Study 24, 1.244; Study 25, 1.249; Study 39, 1.472; Study 40, 1.200.
Analysis with imputation (FAS).

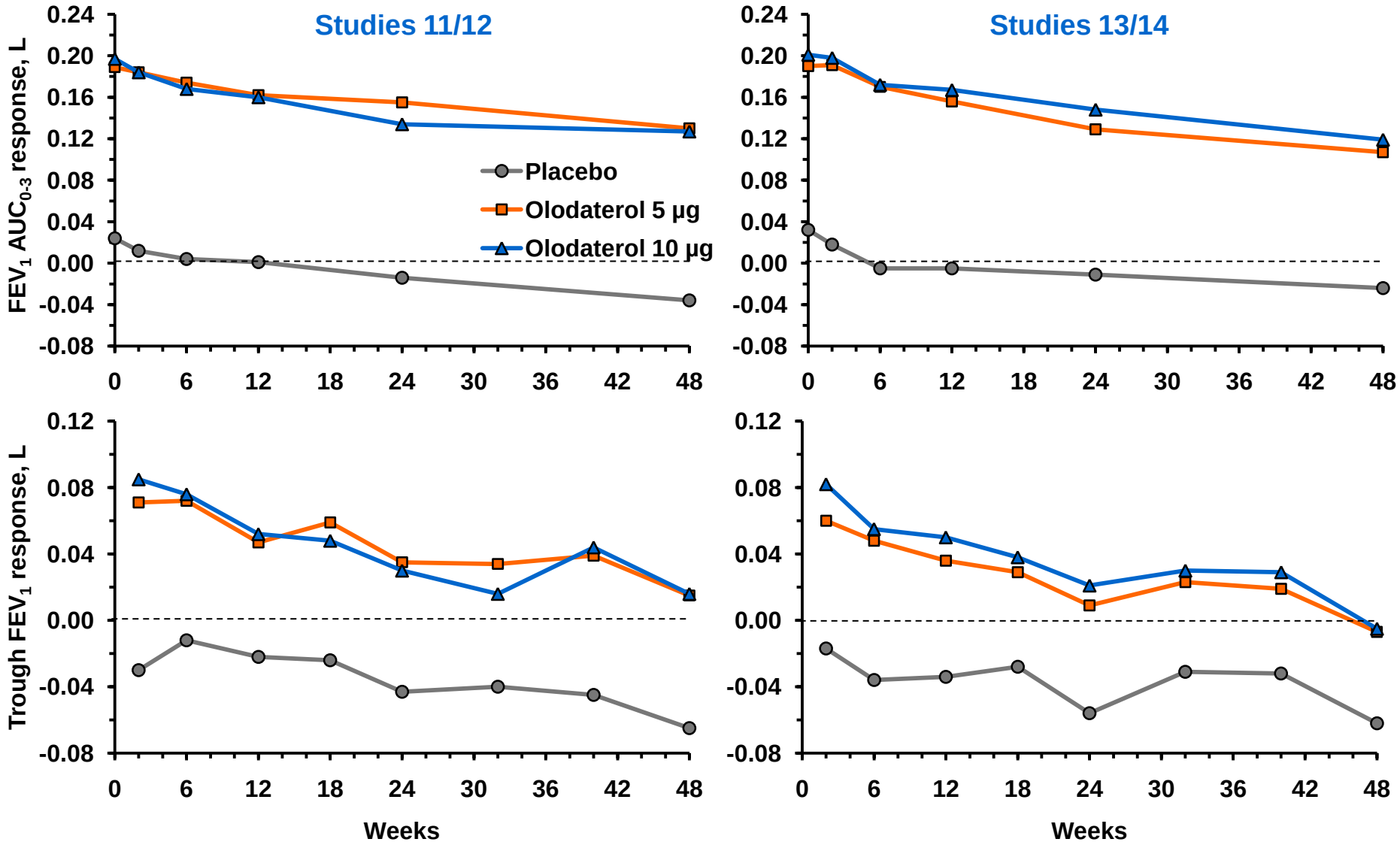
Adjusted Mean FEV_1 Over 24 hr After 6 Weeks



Common baseline mean: Study 24, 1.244; Study 25, 1.249; Study 39, 1.472; Study 40, 1.200.
Analysis with imputation (FAS).

5 µg Once Daily vs 10 µg Once Daily

Adjusted Mean FEV_1 AUC_{0-3} and Trough FEV_1 Response Over 48 Weeks



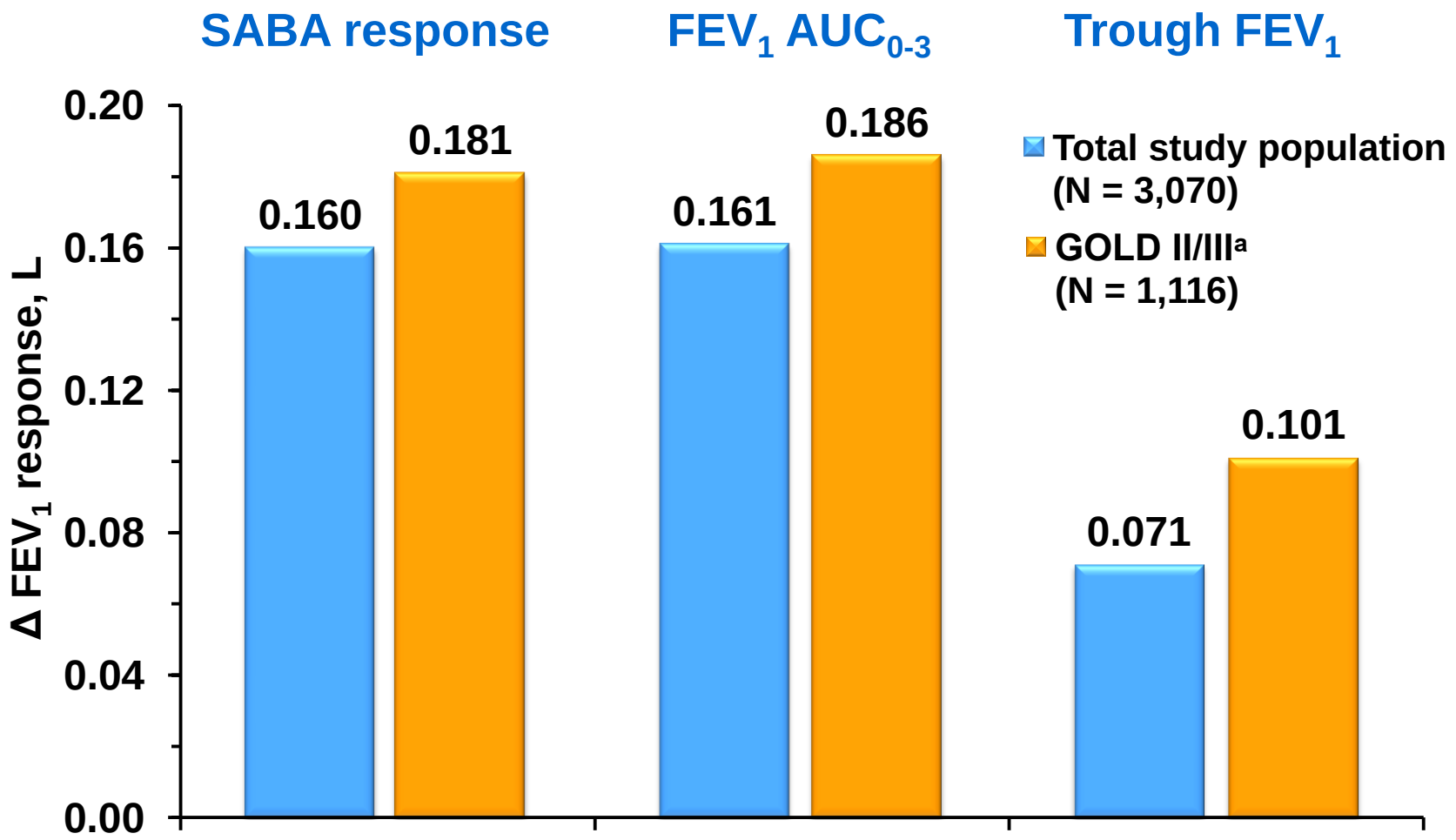
Common baseline mean (SE): Studies 11/12: 1.145 (0.014); Studies 13/14: 1.208 (0.011). Analysis with imputation (FAS).

Effect Size: Trial Design Considerations

FEV_1 $AUC_{0\text{-}3}$ and Trough FEV_1 Response

Olodaterol Pivotal Studies

GOLD II/III Patients Not on Background Therapy



Studies 11-14 pooled dataset.

[a] No SAMA/No LAMA/No xanthine/No beta-blocker.

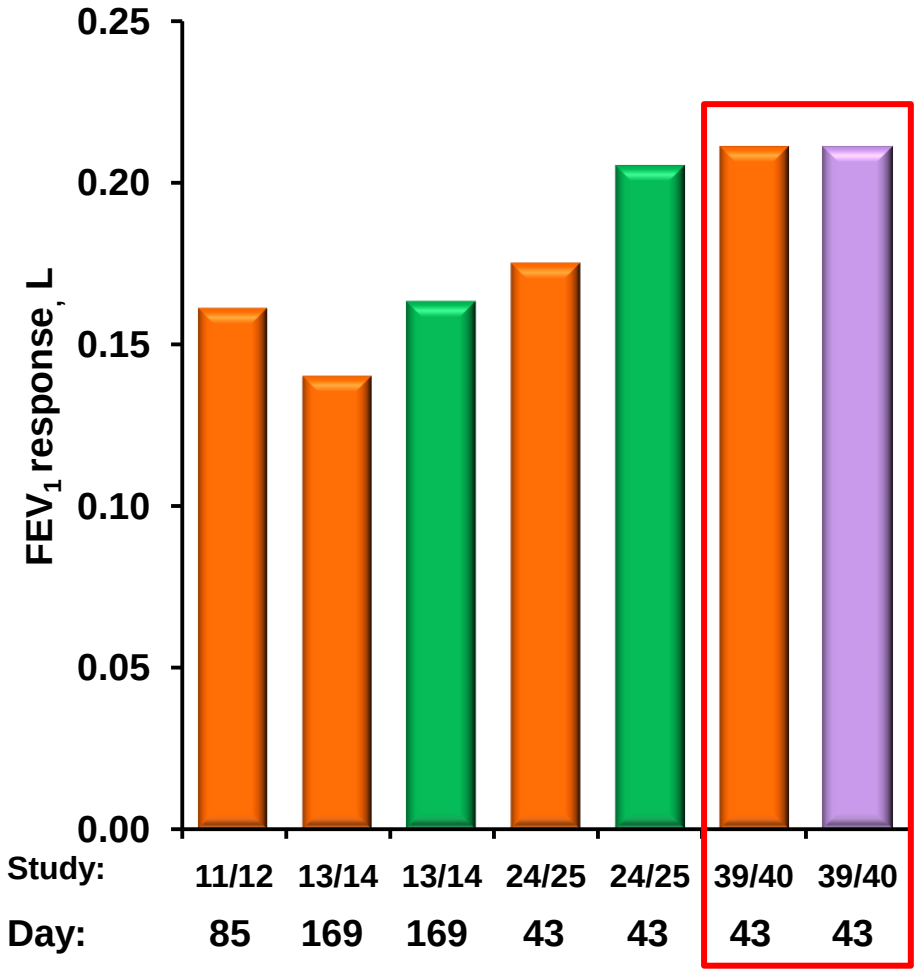
Olodaterol Phase III Studies

	Pivotal studies		24-hour studies	
Studies	**11/12**	**13/14**	**24/25**	**39/40**
Baseline FEV_1, L	1.180	1.249	1.241	1.350
SABA responsiveness, L (%)	0.167 (16.1)	0.155 (14.3)	0.187 (16.8)	0.203 (17.7)
SAMA, % patients	18.9	29.1	16.1	**Not allowed**
LAMA, % patients	21.1	25.7	24.1	**Not allowed**
ICS, % patients	40.9	48.5	31.2	49.1
Xanthines, % patients	12.7	17.7	0.5	7.0
Timing of trough FEV_1	Pre-dose	Pre-dose	24-hr post-dose	24-hr post-dose
Timing of tiotropium dosing before trough	24 hr	24 hr	48 hr	NA

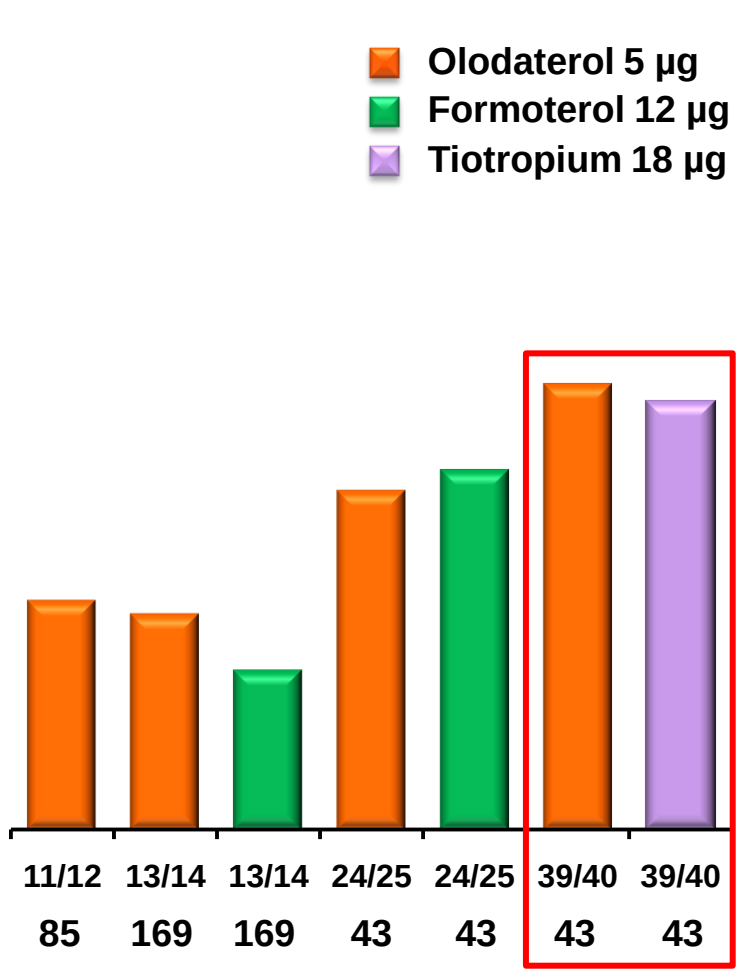
FEV_1 AUC_{0-3} and Trough FEV_1 Responses

Difference vs Placebo Across Studies

FEV_1 AUC_{0-3} response



Trough FEV_1 response



Olodaterol 5 µg Once Daily
Lung Function Efficacy: Summary

- Pivotal studies
  - Rapid onset, comparable to formoterol (Day 1)
  - FEV_1 $AUC_{0\text{-}3}$ response, trough FEV_1 response
    - Significant increase vs placebo (4 studies)
    - Comparable with olodaterol 10 µg once daily
    - Comparable with formoterol 12 µg twice daily
  - Significant lung function improvements up to 48 weeks
- 24-hour bronchodilating profile
  - Comparable with olodaterol 10 µg once daily
  - Comparable with tiotropium HandiHaler 18 µg once daily

Outline of Presentation

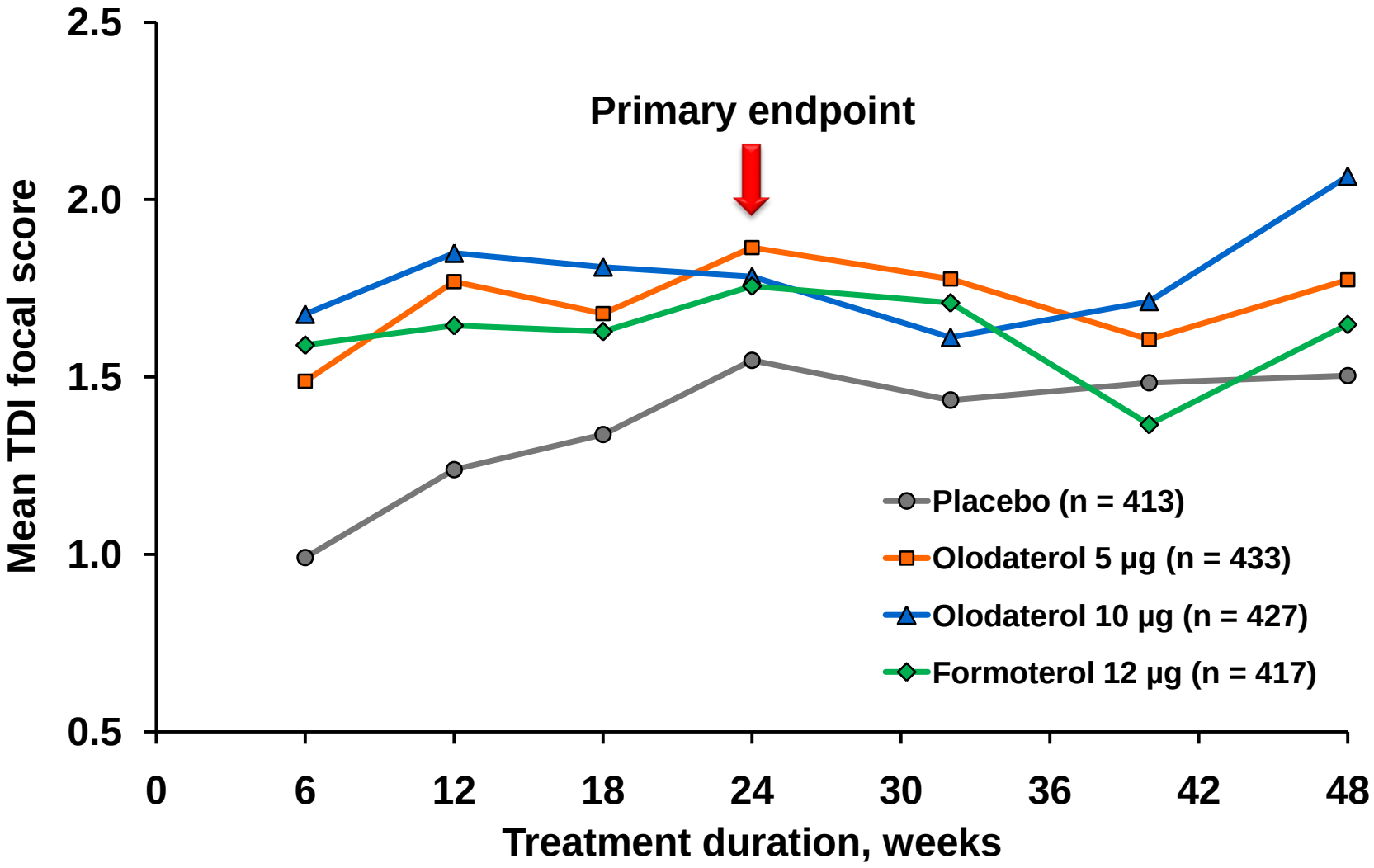
- Overview of clinical program
- Phase II (COPD and asthma)
- Phase III (COPD)
  - Primary evidence of efficacy (olodaterol 5 µg qd)
- Supportive evidence of efficacy: symptomatic benefit
  - TDI, SGRQ, rescue medication use
- Exercise tolerance

Symptom-Based Endpoints

- Mahler Baseline/Transition Dyspnea Index (BDI/TDI)
  - Studies 13 and 14 (combined dataset; co-primary endpoint)
- St. George's Respiratory Questionnaire (SGRQ)
  - Studies 13 and 14 (combined dataset; key secondary endpoint)
- Daytime and nighttime rescue medication use
  - Studies 11 and 12, Studies 13 and 14

TDI Focal Score

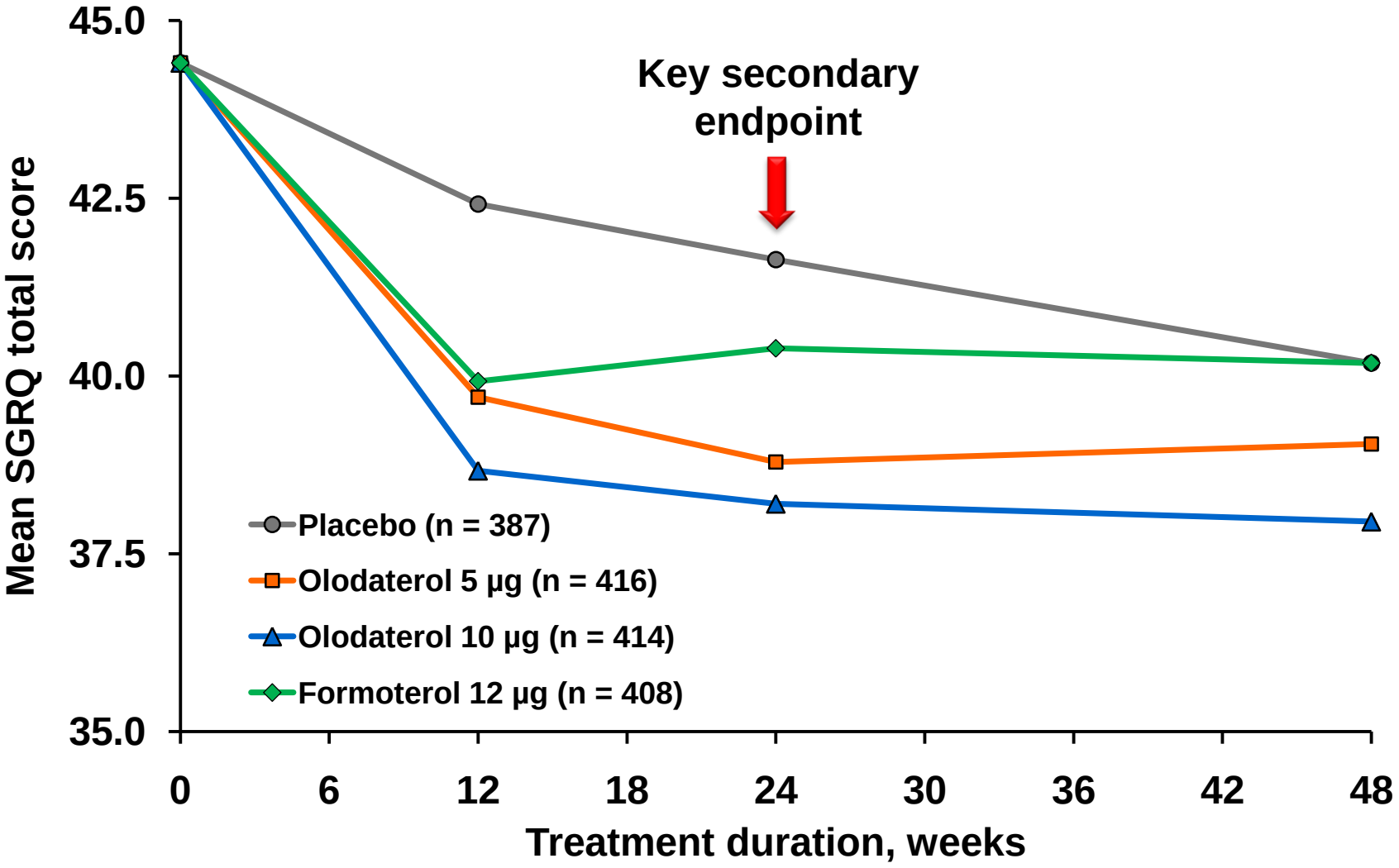
Studies 13 and 14 (Combined Dataset)



BDI, common baseline mean (SE): 6.743 (0.058).

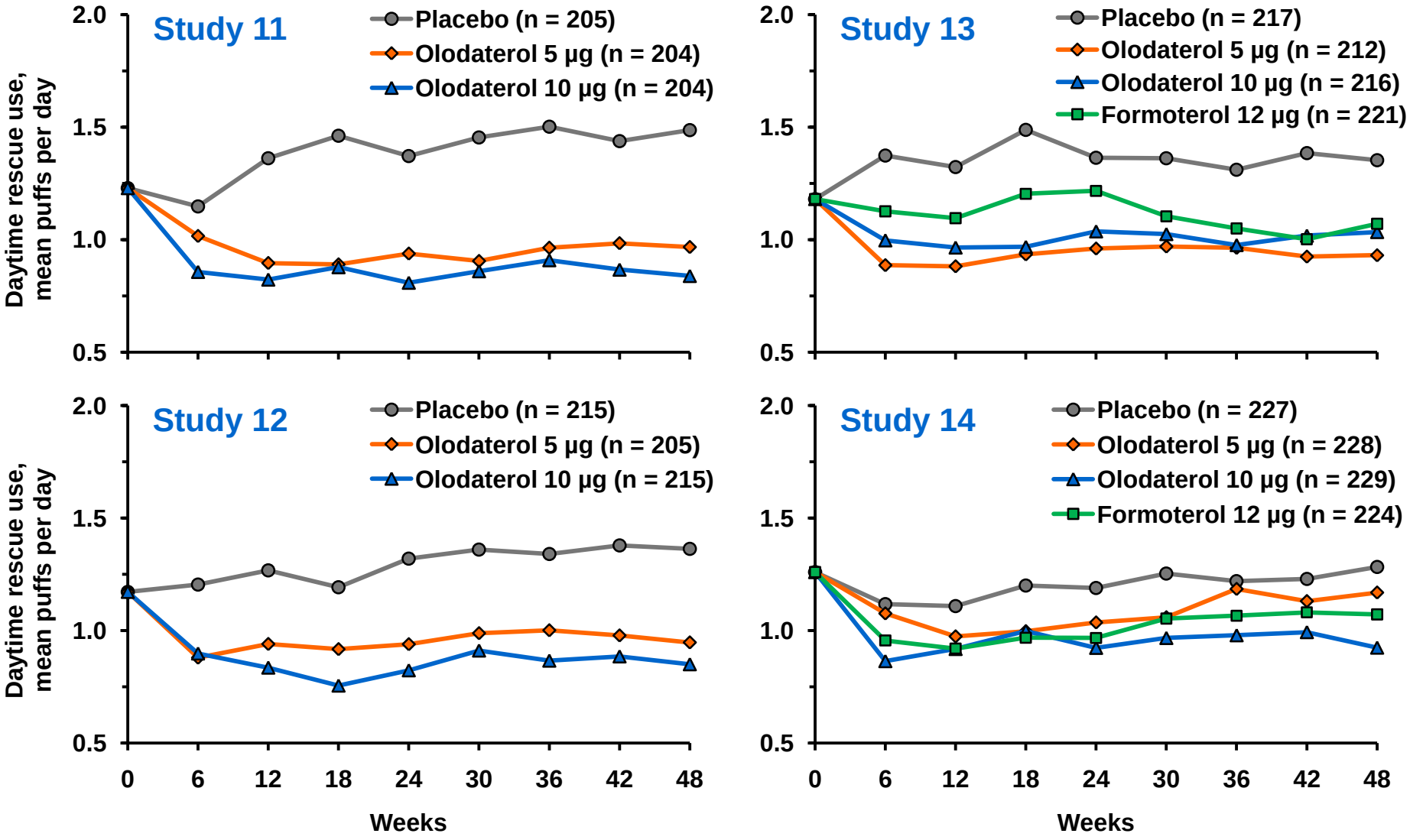
SGRQ Total Score

Studies 13 and 14 (Combined Dataset)



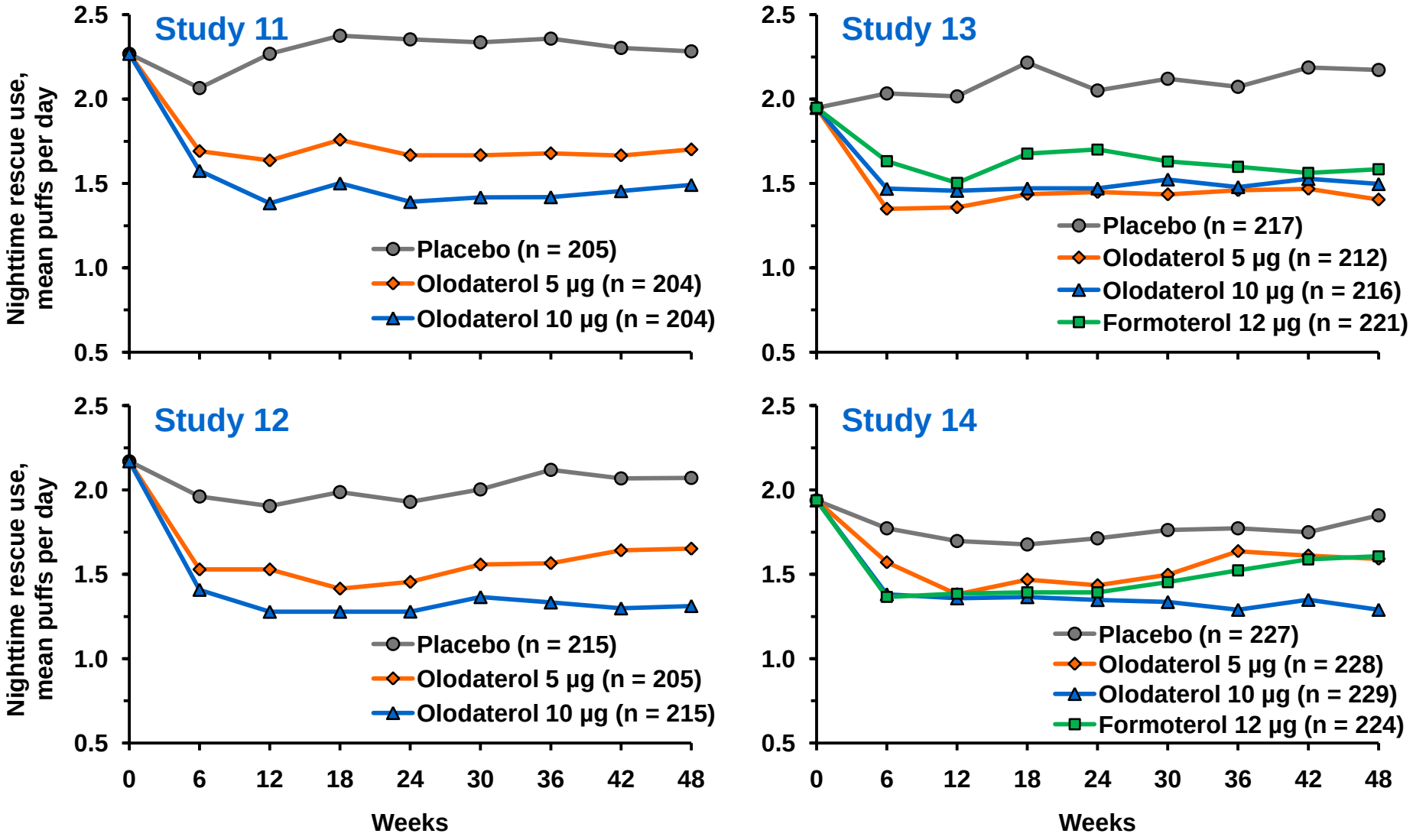
Common baseline mean (SE) = 44.4 (0.47).
MCID (minimal clinically important difference): 4 units.

Daytime Rescue Medication Use



Analysis with imputation (FAS).

Nighttime Rescue Medication Use



Analysis with imputation (FAS).

Olodaterol 5 µg Once Daily
Efficacy Summary

- In each of 4 pivotal studies, olodaterol 5 µg once daily significantly improved lung function (FEV_1 AUC_{0-3}, trough FEV_1) versus placebo
- In placebo- and active-controlled studies, improvements in lung function for olodaterol 5 µg once daily were comparable with once-daily LAMA (tiotropium) and twice-daily LABA (formoterol)
- In all Phase III studies, lung function efficacy of olodaterol 5 µg once-daily was comparable with olodaterol 10 µg once daily
- Effect sizes were in line with expectations for a once-daily bronchodilator
- Lung function improvements translated into symptomatic benefit

- **Conclusion:** The Phase III clinical program provides substantial evidence that once-daily treatment with olodaterol 5 µg leads to clinically meaningful bronchodilation in patients with moderate to very severe COPD

Outline of Presentation

- Overview of clinical program
- Phase II (COPD and asthma)
- Phase III (COPD)
  - Primary evidence of efficacy (olodaterol 5 µg qd)
- Supportive evidence of efficacy: symptomatic benefit
  - TDI, SGRQ, rescue medication use
- Exercise tolerance

Exercise Tolerance
Studies 37 and 38

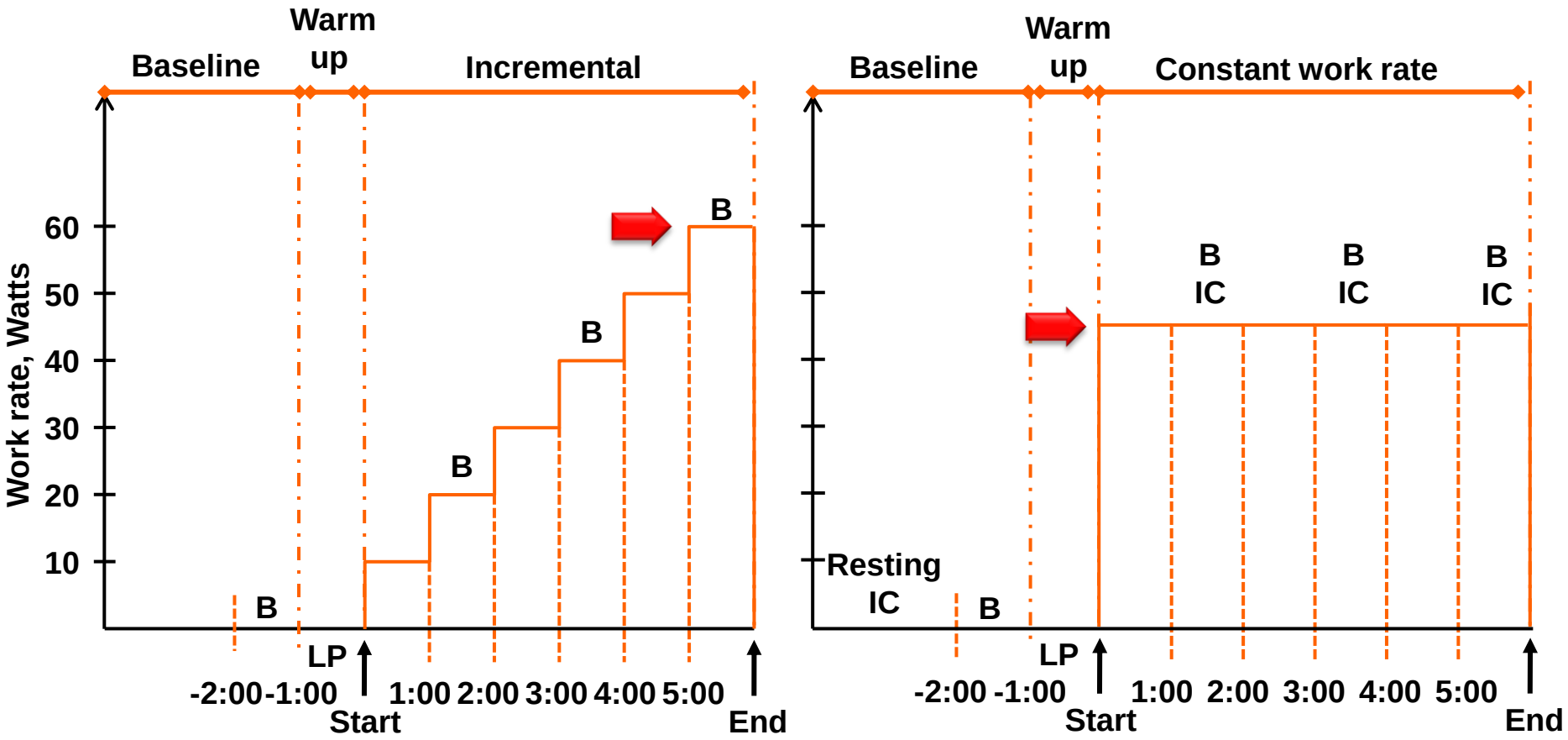
- Constant work rate cycle ergometry at 75% of maximal work capacity (Wcap)
- 6-week, randomized, double-blind, placebo-controlled, 3-period, crossover studies
  - Olodaterol 5 µg once daily
  - Olodaterol 10 µg once daily
- Primary endpoint
  - Symptom-limited endurance time (log transformed)
- Secondary endpoints
  - Inspiratory capacity at isotime
  - Intensity of breathing discomfort at isotime (Borg scale)

Patient Population
Studies 37 and 38

- Diagnosis of COPD
- Post-bronchodilator spirometry
  - FEV_1 < 80% predicted (GOLD II/III/IV)
  - FEV_1/FVC < 70%
- Male or female, 40 to 75 years
- Current/ex-smoker
  - Smoking history ≥ 10 pack-years
- *No requirement for lung hyperinflation*

Cycle Ergometry

Incremental and Constant Work Rate



LP = loadless pedaling; B = Borg scale; IC = inspiratory capacity.

Visit Schedule
Studies 37 and 38

				Treatment period								Follow-up
	Screening/Baseline			Period 1			Period 2			Period 3		
Visit	0	1	2	3	4		5	6		7	8	9
Week of treatment	—	—	—	0	6	14-day wash out	0	6	14-day wash out	0	6	—
Day of treatment	—	—	—	1	43		1	43		1	43	—
Week (cumulative)		–2	–1	0	6		8	14		16	22	24
Day (cumulative)		–14	–7	1	43		57	99		113	155	V8+14

ICE/Practice CWR

Baseline CWR

Randomization

CWR

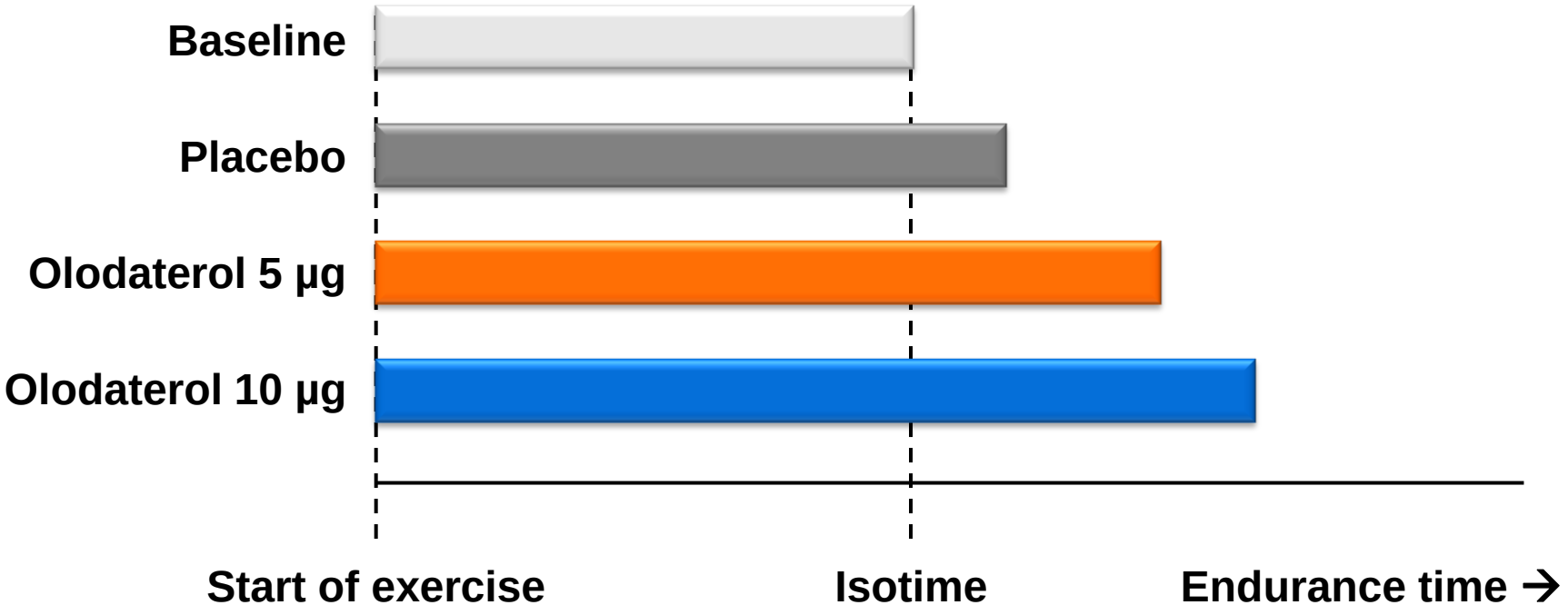
CWR

CWR

2 hrs post-dose

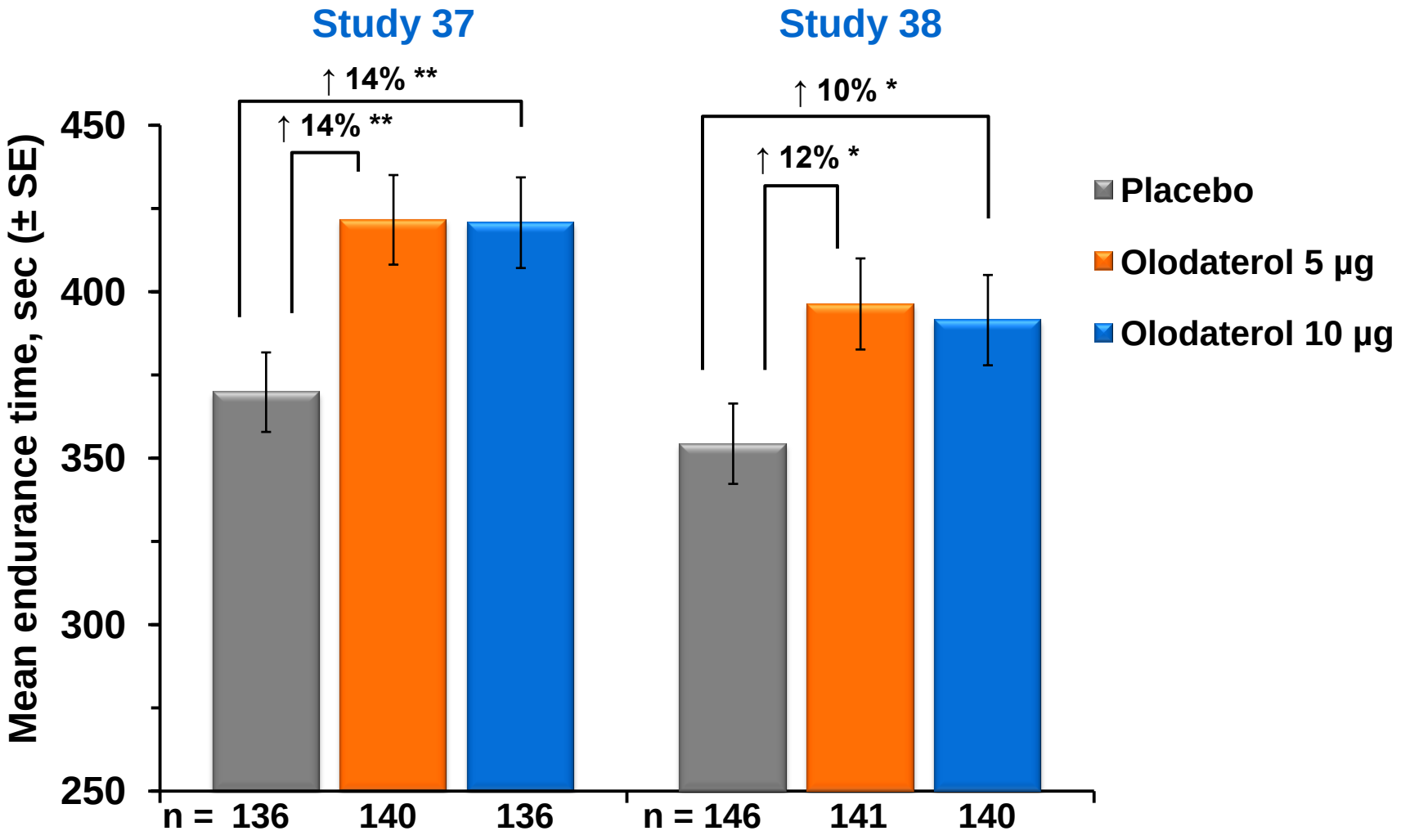
Cycle Ergometry at 75%Wcap

Isotime Determination



Cycle Ergometry at 75%Wcap

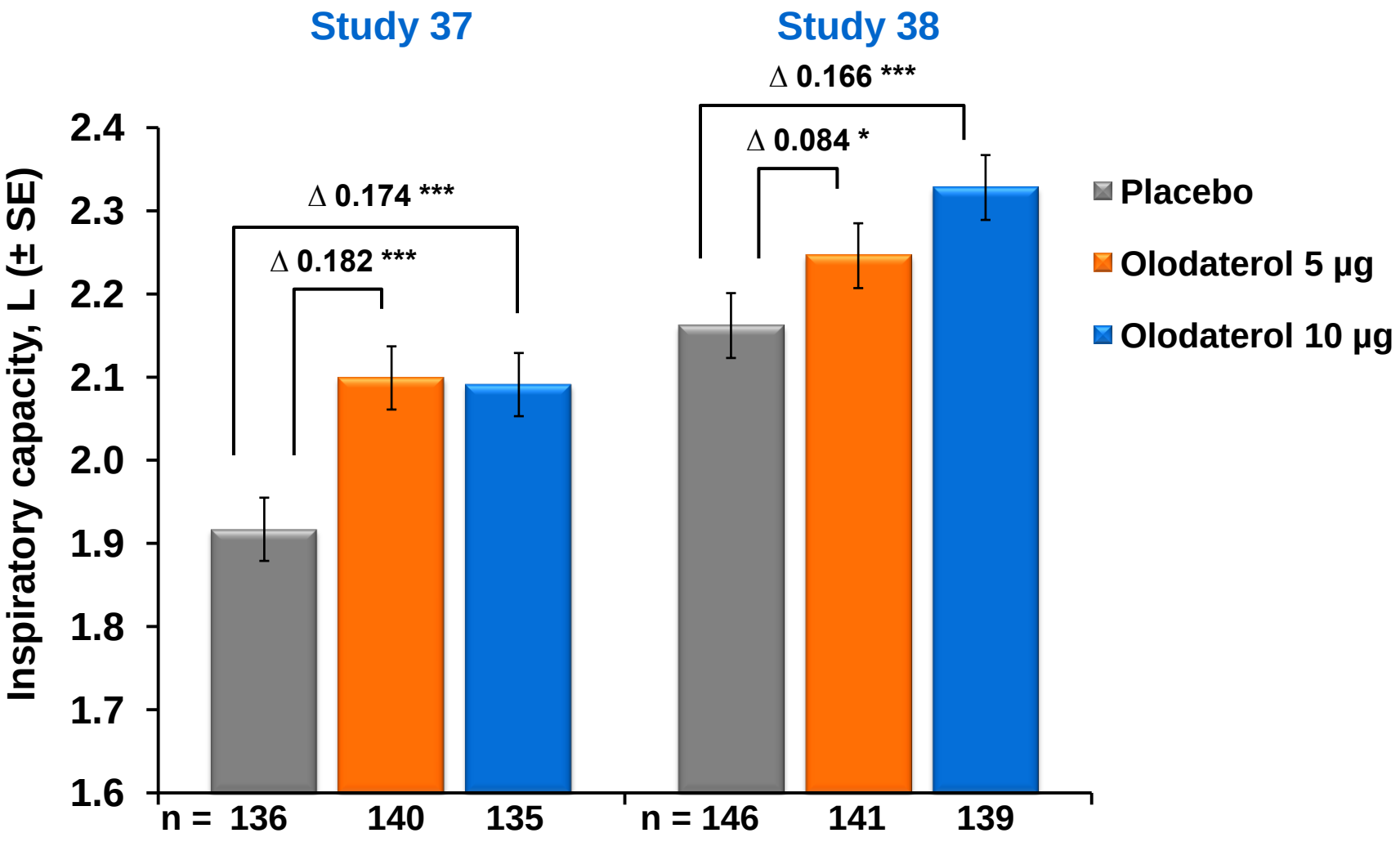
Symptom-limited Endurance Time



Baseline endurance time.
* $p < 0.05$; ** $p < 0.001$ for difference from placebo.

Cycle Ergometry at 75%Wcap

Inspiratory Capacity at Isotime

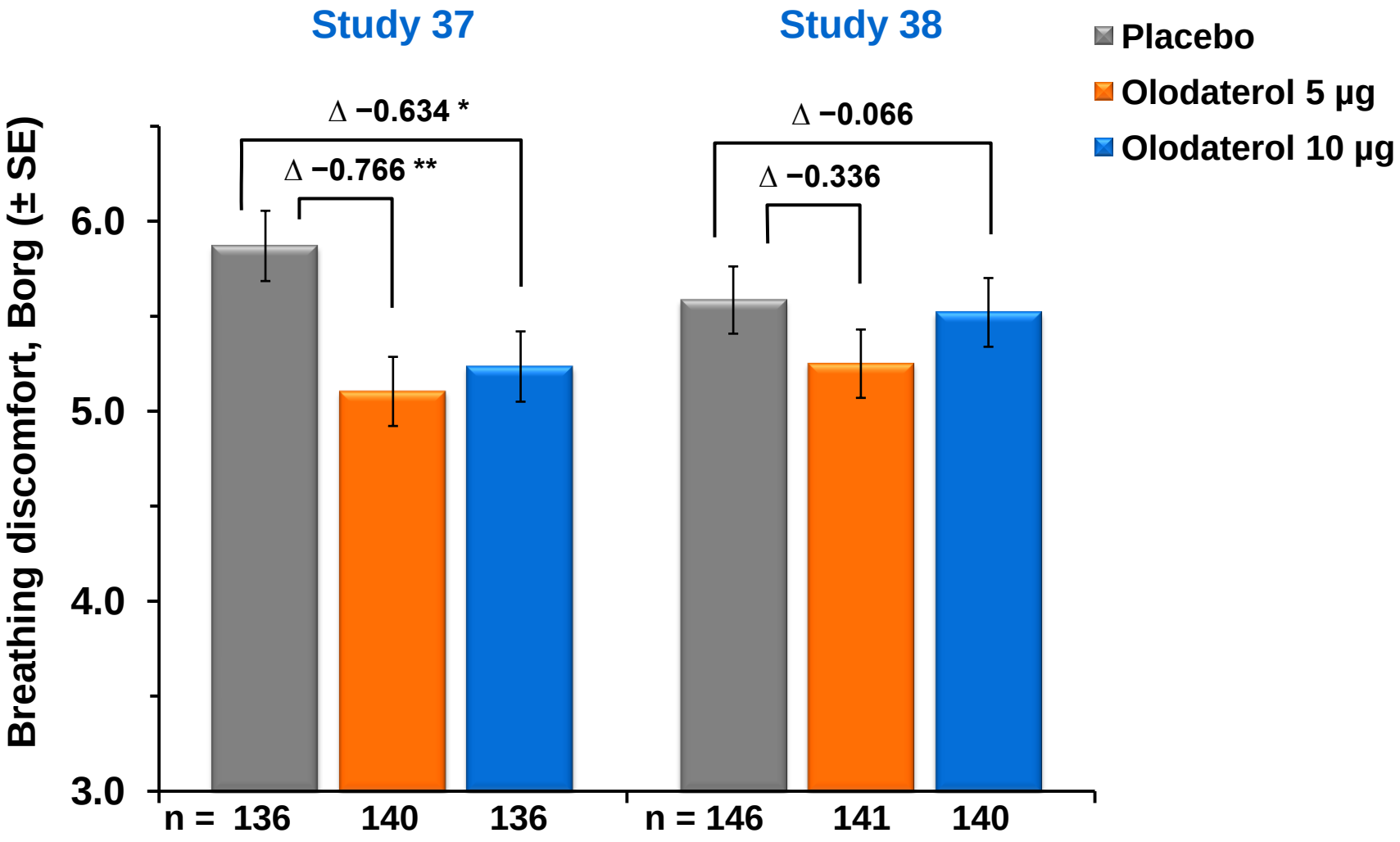


Baseline.

* $p < 0.05$; *** $p < 0.0001$ for difference from placebo.

Cycle Ergometry at 75%Wcap

Breathing Discomfort at Isotime



Baseline.

* $p < 0.05$; ** $p < 0.001$ for difference from placebo.

Exercise Tolerance Studies
Conclusions

- Improvements in airflow limitation translated into reduced lung hyperinflation during exercise
- Reduced lung hyperinflation during exercise resulted in significant improvements in symptom-limited exercise endurance time
- These data provide important additional information to further characterize the bronchodilator efficacy of olodaterol

Package Insert
Proposed Wording

14.1: CLINICAL STUDIES – Additional Trials

The effect of STRIVERDI RESPIMAT 5 mcg on symptom-limited exercise tolerance in COPD patients was investigated in two replicate, randomized, double-blind, placebo-controlled, 6-week cross-over trials.

In these trials, STRIVERDI RESPIMAT 5 mcg significantly improved exercise endurance time by 14.0% (p = 0.0002) and 11.8% (p = 0.0018) compared to placebo.

During exercise, STRIVERDI RESPIMAT 5 mcg increased inspiratory capacity (IC) compared to placebo, indicative of a reduction in lung hyperinflation.

Safety and Risk Management of Olodaterol for COPD

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Head, Therapeutic Area Respiratory Diseases
Boehringer Ingelheim

Boehringer Ingelheim

Safety Overview

- Safety Population, Demographics, Disposition
- Adverse Events by Preferred Term and Aggregated Terms
- Areas of Special Interest:
  - Cardiovascular Events/MACE
  - Respiratory Cause SAEs
  - Neoplasms
- Clinical Laboratory, Class- and Administration-Related AEs
- Subgroup Analysis (Extrinsic + Intrinsic Factors)
- Safety in Phase II/Asthma
- Risk Evaluation and Management for Olodaterol

Methods

- Standard adverse event reporting and evaluation by preferred term (PT) and pre-defined aggregated terms (SMQ, PV)
- Blinded adjudication of all serious respiratory adverse events by adjudication committee (FDA advice)
- Mortality
  - Complete vital status follow-up for planned duration
  - Adjudication of all deaths (MAC)
- Cardiovascular safety
  - ECGs for all patients and Holter monitoring in 772 patients at weeks 6, 12, 24, and 48
- Administration-related paradoxical reaction

Safety Populations

Primary long-term safety database in COPD:

- 2 pairs of replicate 48-week studies (N = 3104)

Extent of exposure, n	Placebo n = 885	Olodaterol 5 µg n = 876	Olodaterol 10 µg n = 883	Formoterol 12 µg n = 460
≥ 85 days	793	833	828	420
≥ 169 days	748	792	798	403
≥ 330 days	686	741	733	376
≥ 337 days	469	504	510	259
Mean	288	308	305	299

Supportive safety in COPD, asthma and healthy volunteers:

- 3 pairs of 6-week crossover studies in COPD (N = 737)
- Phase I + II in healthy volunteers (N = 276) and COPD (N = 1,095)
- Phase II asthma studies (N = 731)

Demographics of 48-week Studies
Safety Population

	Placebo n = 885	Olodaterol 5 µg n = 876	Olodaterol 10 µg n = 883	Formoterol 12 µg n = 460
Sex, %				
Male	76.7	76.0	74.9	80.7
Female	23.3	24.0	25.1	19.3
Age, yr				
Mean (range)	64.3 (40 - 85)	64.0 (40 - 88)	64.2 (40 - 87)	64.9 (40 - 89)
Race, %				
White	66.0	65.9	66.1	68.9
Black/African American	1.2	1.5	1.5	0.4
Asian	32.2	32.1	32.2	30.4
Other	0.6	0.6	0.2	0.2
Smoking history				
Ex-smoker, %	62.0	62.4	63.1	66.3
Smoker, %	38.0	37.6	36.9	33.7
Pack-years, mean (range)	45.8 (10 - 222)	46.6 (10 - 336)	46.6 (10 - 480)	45.1 (10 - 215)

Disease Characteristics at Screening[a]

48-week Studies in COPD

	Placebo n = 885	Olodaterol 5 µg n = 876	Olodaterol 10 µg n = 883	Formoterol 12 µg n = 460
Pre-bronchodilator				
Mean FEV_1, L (range)	1.22 (0.36 - 2.93)	1.22 (0.39 - 2.98)	1.21 (0.35 - 3.04)	1.24 (0.47 - 3.00)
% predicted	44.3	44.4	44.0	45.8
Post-bronchodilator				
GOLD,[b] %				
Stage I	0.2	0.2	0.1	0.7
Stage II	50.7	51.5	47.0	53.7
Stage III	36.8	38.9	43.8	37.4
Stage IV	12.2	9.4	9.1	8.3

[a] **Treated set.**

[b] **Based on post-bronchodilator FEV_1.**

Co-medication & Comorbidities at Screening

48-week Studies in COPD

	Placebo n = 885	Olodaterol 5 µg n = 876	Olodaterol 10 µg n = 883	Formoterol 12 µg n = 460
Medication at baseline, %				
Inhaled steroids	46.0	45.0	45.1	45.7
LABA	35.7	35.6	38.4	37.6
SAMA	24.9	25.0	22.8	28.9
LAMA	23.6	22.1	24.8	25.4
Xanthines	15.0	16.2	14.8	17.4
Any cardiovascular med	63.4	66.9	65.3	64.6
β-blocker	10.5	9.6	9.9	7.5
Selected co-morbidities at baseline, %				
Cardiac disorder	23.1	25.0	25.9	20.0
Cardiac arrhythmia	13.0	13.6	13.1	9.1
Coronary artery disease	9.4	11.6	12.3	9.8
History of neoplasms	6.2	9.2	7.2	2.8

Patient Disposition
48-week Studies in COPD

	Patients, %			
	Placebo	Olodaterol 5 µg	Olodaterol 10 µg	Formoterol 12 µg
Treated	100	100	100	100
Prematurely discontinued from trial medication	22.5	15.1	16.5	18.0
Adverse event	8.8	6.7	7.6	7.8
Respiratory, thoracic and mediastinal disorders	3.6	3.0	2.6	3.7
AE-study disease worse	3.7	3.1	1.6	2.8
AE-other disease worse	0.8	0.7	0.9	0.7
AE-other	4.3	3.0	5.1	4.4
Lack of efficacy	4.5	1.4	0.8	1.1
Administrative	7.1	5.0	6.0	7.6
Other	2.0	1.9	2.2	1.5

Safety Overview

- Safety Population, Demographics, Disposition
- Adverse Events by Preferred Term and Aggregated Terms
- Areas of Special Interest:
  - Cardiovascular Events/MACE
  - Respiratory Cause SAEs
  - Neoplasms
- Clinical Laboratory, Class- and Administration-Related AEs
- Subgroup Analysis (Extrinsic + Intrinsic Factors)
- Safety in Phase II/Asthma
- Risk Evaluation and Management for Olodaterol

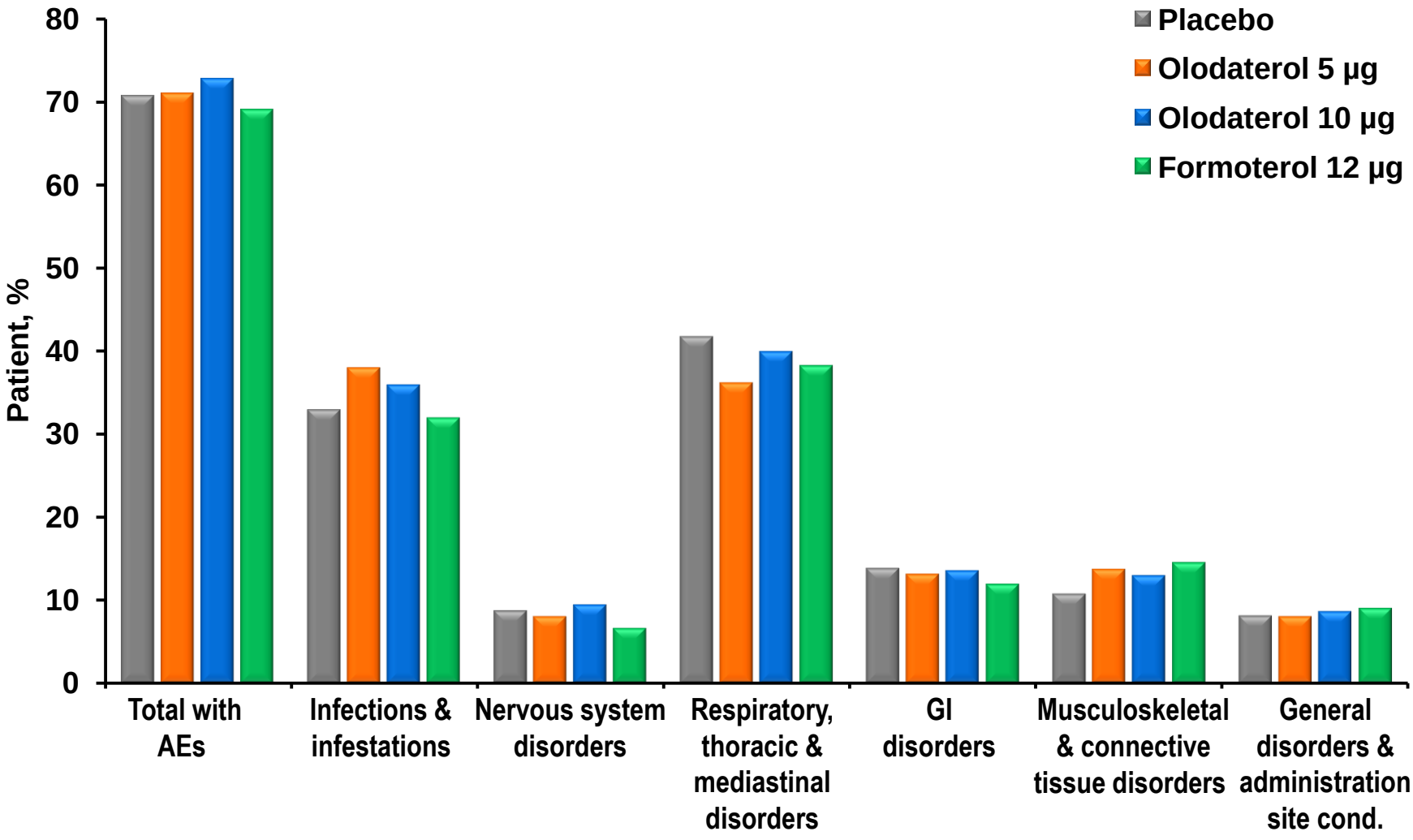
Overview of Adverse Events

48-week Studies in COPD, On-treatment Including 12-day Washout

	Patients, %			
	Placebo n = 885	Olodaterol 5 µg n = 876	Olodaterol 10 µg n = 883	Formoterol 12 µg n = 460
Patients with any AE (%)	**70.8**	**71.0**	**72.7**	**69.1**
Severe AEs	13.2	12.4	13.5	12.4
Investigator-defined related AEs	8.9	7.2	5.9	11.3
Serious AEs	16.4	15.8	16.6	15.0
Fatal (on treatment), % (N)	1.5 (13)	1.5 (13)	1.9 (17)	2.2 (10)
Immediately life-threatening	1.0	0.7	1.0	1.3
Disability/incapacity	0.1	0.1	0.5	0.7
Requires hospitalization	14.5	13.9	14.9	11.3
Prolongs hospitalization	0.6	0.5	1.0	0.7
Other	1.5	1.3	1.1	1.7

Adverse Events ≥ 2% in Olodaterol

48-week Studies in COPD



[a] On-treatment including 12-day washout period unless specified otherwise.

Adverse Events ≥ 2% in Olodaterol
48-week Studies in COPD

System organ class and PTs	Patients, %			
	Placebo n = 885	Olodaterol 5 µg n = 876	Olodaterol 10 µg n = 883	Formoterol 12 µg n = 460
Total with AEs	70.8	71.0	72.7	69.1
Infections and infestations	**33.0**	**38.0**	**35.9**	**32.0**
Nasopharyngitis[a]	7.7	11.3	10.3	10.0
Upper respiratory tract infection	7.5	8.2	7.0	7.0
Bronchitis	3.6	4.7	3.5	2.8
Pneumonia	2.7	2.5	4.0	3.0
Urinary tract infection	1.0	2.5	1.8	1.1

[a] Nasopharyngitis identified as adverse drug reaction.

Adverse Events ≥ 2% in Olodaterol

48-week Studies in COPD

System organ class and PTs	Patients, %			
	Placebo n = 885	Olodaterol 5 µg n = 876	Olodaterol 10 µg n = 883	Formoterol 12 µg n = 460
Total with AEs	70.8	71.0	72.7	69.1
Respiratory, thoracic and mediastinal disorders	**41.8**	**36.2**	**39.9**	**38.3**
Chronic obstructive pulmonary disease	28.8	25.9	30.1	28.5
Cough	4.0	4.2	4.0	5.9

Adverse Events ≥ 2% in Olodaterol
48-week Studies in COPD

System organ class and PTs	Patients, %			
	Placebo n = 885	Olodaterol 5 µg n = 876	Olodaterol 10 µg n = 883	Formoterol 12 µg n = 460
Total with AEs	70.8	71.0	72.7	69.1
Musculoskeletal and connective tissue disorders	**10.8**	**13.8**	**13.0**	**14.6**
Back pain	2.7	3.5	3.2	3.9
Arthralgia[a]	0.8	2.1	1.6	1.3
Muscle spasms	1.2	1.4	0.9	2.2

[a] Arthralgia identified as adverse drug reaction.

Serious Adverse Events by SOC—≥ 2 Patients by Preferred Term

48-week Studies in COPD

	Patients, %			
System organ class	Placebo n = 885	Olodaterol 5 µg n = 876	Olodaterol 10 µg n = 883	Formoterol 12 µg n = 460
Total with SAEs	**16.4**	**15.8**	**16.6**	**15.0**
Respiratory, thoracic and mediastinal disorders	7.2	5.5	7.9	6.7
Infection and infestations	3.5	3.9	3.6	2.8
Cardiac disorders	2.9	2.2	1.9	1.5
Neoplasms benign, malignant and unspecified[a]	1.0	1.6	2.2	1.7
Injury, poisoning and procedural complications	1.0	1.4	1.8	1.1
Gastrointestinal disorders	1.1	0.6	1.2	1.1
Nervous system disorders	1.5	1.1	0.6	0
General disorders and administration site conditions	0.8	0.9	0.8	1.1
Vascular disorders	0.9	0.9	0.6	0.9
Musculoskeletal and connective tissue disorders	0.3	1.0	1.2	0.9
Hepatobiliary disorders	0.3	0.1	0.5	0
Metabolism and nutrition disorders	0.2	0.3	0.3	0
Reproductive system and breast disorders	0.1	0.1	0.1	0.4

[a] **Including cysts and polyps.**

Adverse Events Leading to Death

Fatal adverse events, n (%)	Placebo	Olodaterol 5 µg	Olodaterol 10 µg	Formoterol 12 µg
Total in all studies (on-treatment, post-treatment and post-study)	23	20	25	13
On-treatment in Phase II and crossover studies in COPD	—	1	4[a]	—
Healthy volunteer or asthma studies	—	—	—	—

N treated in 48-week trials in COPD	885	876	883	460
Total on-treatment in 48-week trials	13 (1.5)	13 (1.5)	17 (1.9)	10 (2.2)
Post-treatment or post-study	10	6	4	3
Post-study after planned observation period[b] [Day 337 + 14-day washout = Day 351]	—	1	3	3
Total reported in 48-week trials	23 (2.6)	19 (2.2)	21 (2.4)	13 (2.8)
Total within planned observation period [censored Day 351] [b]	23 (2.6)	18 (2.1)	18 (2.0)	10 (2.2)

[a] Includes 2 fatal events in washout period of 4-week crossover studies.
[b] Planned observation period/censoring rule: treatment planned until Day 337 + 14-day washout = Day 351.
Censored fatal events: Pat.ident. (day stop treatment/day of death): Olo5: Pat 3578 (330/452); Olo10: Pat 6379 (328/357); Pat 3621 (118/383); Pat 6205 (330/378); Formoterol: Pat 10945 (330/378); Pat13286 (330/428); Pat 12066 (330/363).

Fatal Adverse Events, Adjudicated Cause

48-week Studies in COPD, On-Treatment

Adjudicated primary causes of death	Patients, n (%) Placebo n = 885	Olodaterol 5 µg n = 876	Olodaterol 10 µg n = 883	Formoterol 12 µg n = 460
Total with AEs leading to death	13 (1.5)	13 (1.5)	17 (1.9)	10 (2.2)
Respiratory, thoracic and mediastinal disorders: COPD exacerbation	4 (0.5)	9 (1.0)	4 (0.5)	3 (0.7)
Infections and Infestations: Pneumonia	—	—	2 (0.2)	—
Cardiac and vascular disorders incl. sudden death: Sudden death/cardiac death, congestive heart failure, cerebrovascular accident, aortic aneurysm/rupture	6 (0.7)	2 (0.2)	1 (0.1)	4 (0.9)
Neoplasms: Lung ca, larynx ca, esophagus ca, bladder ca, hepatic ca	—	2 (0.2)	7 (0.8)	1 (0.2)
Death, unknown cause	3 (0.3)	—	2 (0.2)	1 (0.2)
Other: Suicide, arthropod bite	—	—	1 (0.1)	1 (0.2)

Safety Overview

- Safety Population, Demographics, Disposition
- Adverse Events by Preferred Term and Aggregated Terms
- Areas of Special Interest:
  - Cardiovascular Events/MACE
  - Respiratory Cause SAEs
  - Neoplasms
- Clinical Laboratory, Class- and Administration-Related AEs
- Subgroup Analysis (Extrinsic + Intrinsic Factors)
- Safety in Phase II/Asthma
- Risk Evaluation and Management for Olodaterol

Major Adverse Cardiovascular Events (MACE)

48-week Studies in COPD

	Major adverse CV event		Fatal CV event	
	n	IR	n	IR
Placebo (n = 885)	24	3.33	6	0.82
Olodaterol 5 µg (n = 876)	10	1.30	3	0.39
Rate ratio (95% CI) Olo/Pbo	**0.39**	(0.19, 0.82)*	**0.47**	(0.12, 1.86)
Olodaterol 10 µg (n = 883)	16	2.10	2	0.26
Rate ratio (95% CI) Olo/Pbo	**0.63**	(0.34, 1.19)	**0.32**	(0.06, 1.55)

MACE composite endpoint:

SOC cardiac (fatal), SOC vascular (fatal), MI (fatal + nonfatal), stroke (fatal + nonfatal), sudden death, cardiac death, sudden cardiac death
Fatal composite excludes non-fatal MI and non–fatal stroke

n = number of patients with an event; IR = incidence rate (per 100 patient-years of time at risk); * $p < 0.05$.

Overview of Cardiac Safety

48-week Studies in COPD, Cardiac SOC and SMQs

	Placebo n = 885		Olo 5 µg n = 876		Olo 5 µg – placebo	Olo 10 µg n = 883		Olo 10 µg – placebo
	n	IR	n	IR	RR (95% CI)	n	IR	RR (95% CI)
MedDRA SOC								
Cardiac disorders SOC	67	9.55	69	9.28	**0.97** (0.70, 1.36)	64	8.61	**0.90** (0.64, 1.27)
User-defined SMQ/PV								
Cardiac arrhythmia terms	37	5.19	49	6.54	**1.26** (0.83, 1.94)	39	5.18	**1.00** (0.64, 1.57)
Tachyarrhythmia terms	30	4.19	31	4.09	**0.99** (0.60, 1.62)	26	3.42	**0.82** (0.48, 1.38)
Ventricular tachyarrhythmias	9	1.24	17	2.22	**1.81** (0.81, 4.03)	12	1.57	**1.27** (0.54, 3.01)
Cardiac failure (narrow)	5	0.69	11	1.43	**2.09** (0.73, 6.04)	7	0.91	**1.32** (0.42, 4.19)
Myocardial infarction (broad)	9	1.24	4	0.52	**0.42** (0.13, 1.36)	12	1.57	**1.27** (0.53, 3.00)
Other ischemic heart disease	15	2.08	10	1.30	**0.63** (0.28, 1.40)	14	1.84	**0.89** (0.43, 1.83)
Palpitations	13	1.80	14	1.83	**1.02** (0.48, 2.16)	19	2.50	**1.40** (0.69, 2.82)
Hypertension	36	5.06	27	3.57	**0.71** (0.43, 1.16)	30	3.99	**0.78** (0.48, 1.28)

IR = incidence rate (per 100 patient-years of time at risk); RR (95% CI) = rate ratio (95% confidence interval).

SAEs Adjudicated for Respiratory Events

All Studies > 7 Days

System organ class	Patients, %			
	Placebo n = 1,409	Olodaterol 5 µg n = 1,401	Olodaterol 10 µg n = 1,457	Formoterol 12 µg n = 541
Patients with adjudicated events	**10.4**	**9.9**	**10.2**	**11.8**
Total respiratory-related events	5.3	4.9	5.9	7.2
Key respiratory-related events	5.2	4.4	5.2	6.7
Asthma-related event	0	0	0	0
COPD-related events	4.8	3.6	4.4	5.9
Pneumonia-related events	0.9	1.1	1.8	1.3
Other respiratory-related events	0.2	0.4	1.0	0.7
Non-respirator-related events	5.6	5.8	5.6	5.2

All SAEs were adjudicated for death, hospitalization and intubation related to asthma, COPD or pneumonia by a central, independent committee. There were 18 studies with 5,387 patients exposed to study drug, including asthma and COPD (87%); no adjudicated SAEs with 5 µg bid.

Exacerbations of COPD and Pneumonia

48-week Studies in COPD, Protocol-defined Endpoint and SMQ/User-defined PV

	Olo 5 µg n = 876	HR[a] (95% CI)	Olo 10 µg n = 883	HR[a] (95% CI)
Protocol-defined exacerbation endpoint	**n = 273**	**0.91 (0.77, 1.08)**	**n = 296**	**1.00 (0.85, 1.18)**

	Placebo n = 885		Olo 5 µg n = 876		Olo 5 µg – placebo	Olo 10 µg n = 883		Olo 10 µg – placebo
	n	IR	n	IR	RR (95% CI)	n	IR	RR (95% CI)
COPD PT	255	42.0	227	34.2	**0.81** (0.68, 0.97)*	266	40.8	**0.97** (0.82, 1.15)
COPD exacerbation PV	261	43.2	231	35.0	**0.81** (0.68, 0.96)*	267	40.9	**0.95** (0.80, 1.12)
COPD exacerbation (broad) PV	287	48.5	279	43.7	**0.90** (0.76, 1.06)	296	46.6	**0.96** (0.82, 1.13)
COPD exacerbation (broad) with pneumonia PV	298	50.7	288	45.3	**0.89** (0.76, 1.05)	308	48.9	**0.96** (0.82, 1.13)

n = number of patients with an event; IR = incidence rate (per 100 patient-years of time at risk); RR (95% CI) = rate ratio (95% confidence interval); * $p < 0.05$.

[a] Cox proportional hazards regression of time to first COPD exacerbation.

Neoplasms
48-week Studies in COPD

	Patients, n (%)			
	Placebo n = 885	Olodaterol 5 µg n = 876	Olodaterol 10 µg n = 883	Formoterol 12 µg n = 460
SAE	9 (1.0)	14 (1.6)	19 (2.2)	8 (1.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
SAE + AE	12 (1.4)	15 (1.7)	22 (2.5)	8 (1.7)
Neoplasms malignant and unspecified				

Frequency of Malignant Neoplasms, Including Unspecified

48-week Studies in COPD, Primary PT

	Placebo	Olodaterol 5 µg	Olodaterol 10 µg	Formoterol 12 µg
Skin ca, skin neoplasm, squamous cell ca, basal cell ca	4	2	2	—
Squamous cell ca	—	—	1	1
Hematologic malignancies (leukemia, lymphoma, diff B-cell lymphoma)	1	1	—	1
Hepatic neoplasm malignant	—	1	1	—
Breast cancer	1	—	—	—
Adrenal neoplasm	—	1[a]	—	—
Sarcoma	—	—	1	—
Spinal cord neoplasm	—	—	1	—

[a] **6233: adrenal neoplasm and keratoakanthoma (benign).**

Frequency of Malignant Neoplasms, Including Unspecified

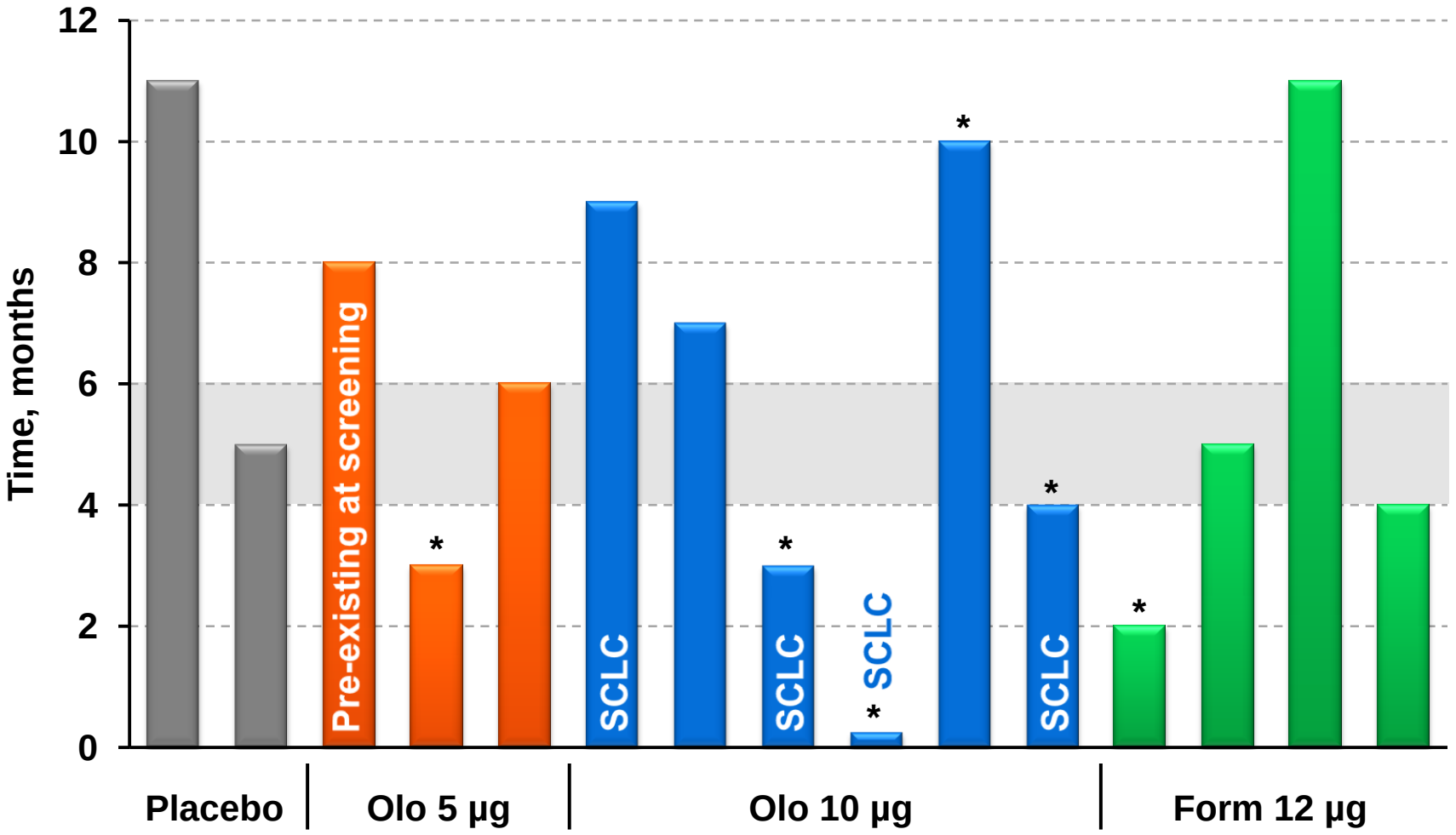
48-week Studies in COPD, Primary (Secondary) PT

	Placebo	Olodaterol 5 µg	Olodaterol 10 µg	Formoterol 12 µg
Lung ca unspec., adenoca, squamous c.ca	2	3	2	4
SCLC unspecified	—	—	4[a]	—
Lung neoplasm, (lung metastases)	1[b]	1[c] (1)[d]	1[e] (2)[f,g]	—
(Liver metastases from SCLC)[a]	—	—	(1)[a]	—
Thyroid neoplasm with lung neoplasm[d]	—	1[d]	2	—
Malignant melanoma with lung neoplasm[f]	—	1	1[f]	—
Bladder cancer with lung metastasis[g]	1	—	2[g]	—
Hypopharyngeal, laryngeal ca	1	—	1	—
Esophageal ca, squamous cell ca	—	1	2	—
Gastric ca, neoplasm	—	2	—	—
Prostate ca, prostate ca recurrent	1	1	1	2

[a] 13736 SCLC with liver metastases; [b] 7397 Lung nodule (possible ca); [c] 4370 lung nodule biopsy negative; [d] 6304 Thyroid neopl. with lung nodule; [e] 6009 lung nodule (possible ca); [f] 3372 Primary malignant melanoma with lung neoplasm; [g] 3621 bladder ca with lung metastasis.

Time to Lung Cancer (Verified PV)

48-week Studies in COPD



* Death on treatment.

Neoplasms
48-week Studies in COPD

	N (incidence rate per 100 patient-years)			
	Placebo n = 885	Olodaterol 5 µg n = 876	Olodaterol 10 µg n = 883	Formoterol 12 µg n = 460
SAE/AE neoplasms malignant and unspecified	12 (1.66)	15 (1.96)	22 (2.89)	8 (2.05)
RR (CI)		**1.18** (0.55, 2.53)	**1.75** (0.86, 3.53)	**1.52** (0.49, 4.66)

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- Risk Evaluation and Management for Olodaterol

Laboratory Anomalies
48-week Registration Studies

- Statistically significant increases in CPK in olodaterol 5 and 10 µg groups vs placebo on individual test days, as well as shifts out of normal range – more pronounced in formoterol group
  - Affected patients did not have increased AEs
- Transient decreases of blood potassium concentrations in healthy volunteer studies starting at doses of 10 to 20 µg olodaterol
- Proportion of patients with potassium values shifted to below the lower limit of normal similar between both olodaterol treatment groups and placebo in the 48-week studies
- Proportion of patients with glucose shift toward outside normal range comparable between treatment groups

Drug Class Related AEs ≥ 2% in Any Group

48-week Studies in COPD

System organ class SMQ, PV endpoints	Patients, % Placebo n = 885	Olodaterol 5 µg n = 876	Olodaterol 10 µg n = 883	Formoterol 12 µg n = 460
Total with AEs	**70.8**	**71.0**	**72.7**	**69.1**
General disorders and administration site conditions				
Accidents & injuries (narrow)	5.9	6.3	7.5	4.1
Chest pain	2.8	1.9	2.3	3.0
Musculoskeletal and connective tissue disorders				
Arthralgia/Myalgia/Muscle weakness	8.7	11.2	10.8	11.3
Nervous system disorders				
Headache	3.6	3.1	3.5	3.5
Dizziness	2.6	2.9	2.9	2.2
Cardiac disorders				
Cardiac arrhythmias	4.2	5.6	4.4	4.3
Cardiac arrhythmias, tachyarrhythmias	3.4	3.5	2.9	3.3
Cardiac arrhythmias, ventricular tachyarrhythmias	1.0	1.9	1.4	2.0
Palpitations	1.5	1.6	2.2	2.2
Vascular disorders				
Hypertension (narrow)	4.1	3.1	3.4	2.2

Respiratory Events Indicative of Paradoxical Reaction Related to Study Drug Administration

CS-31

Studies 11 and 12

	Patients, %		
	Placebo n = 425	Olodaterol 5 µg n = 417	Olodaterol 10 µg n = 424
Drop in FEV_1 ≥ 15% from trough (a)	11.8	2.6	3.8
Rescue medication use within 30 min of inhaling randomized treatment on a clinic test day (b)	2.1	0.2	0.9
Cough, wheeze, or dyspnea AE within 30 min of inhaling randomized treatment on a clinic test day (c)	0	0	0
Any of (a), (b), (c)	13.6	2.9	4.7

Safety Overview

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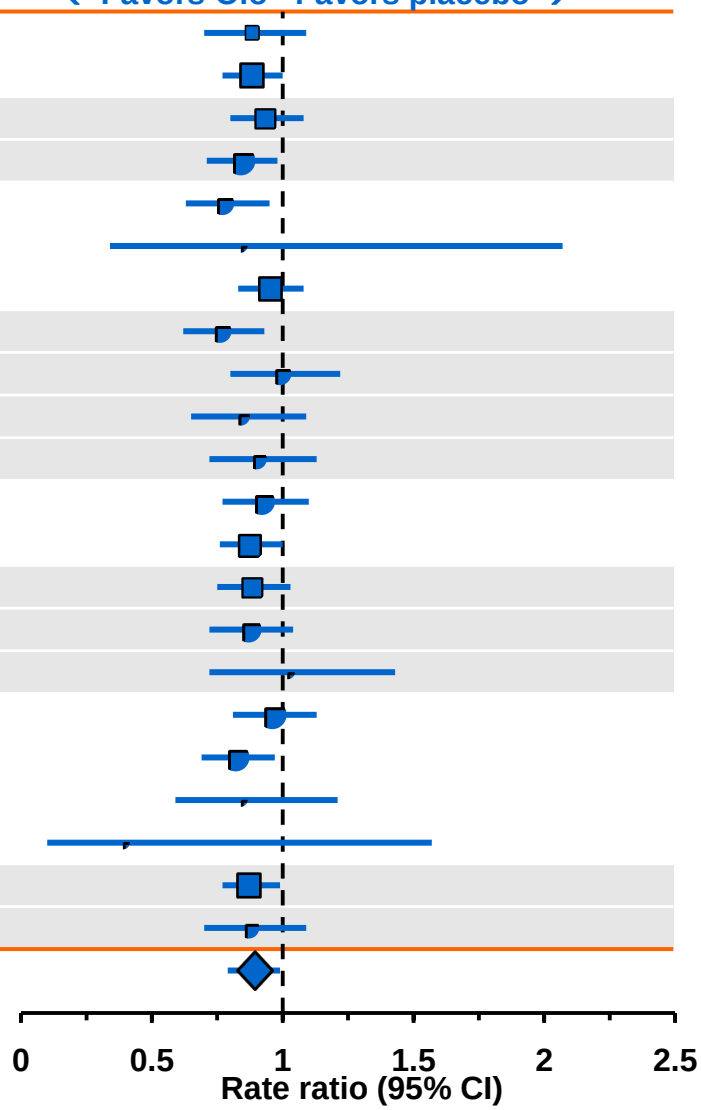
Adverse Event Exposure-adjusted Rate Ratio—Olodaterol 5 µg vs Placebo

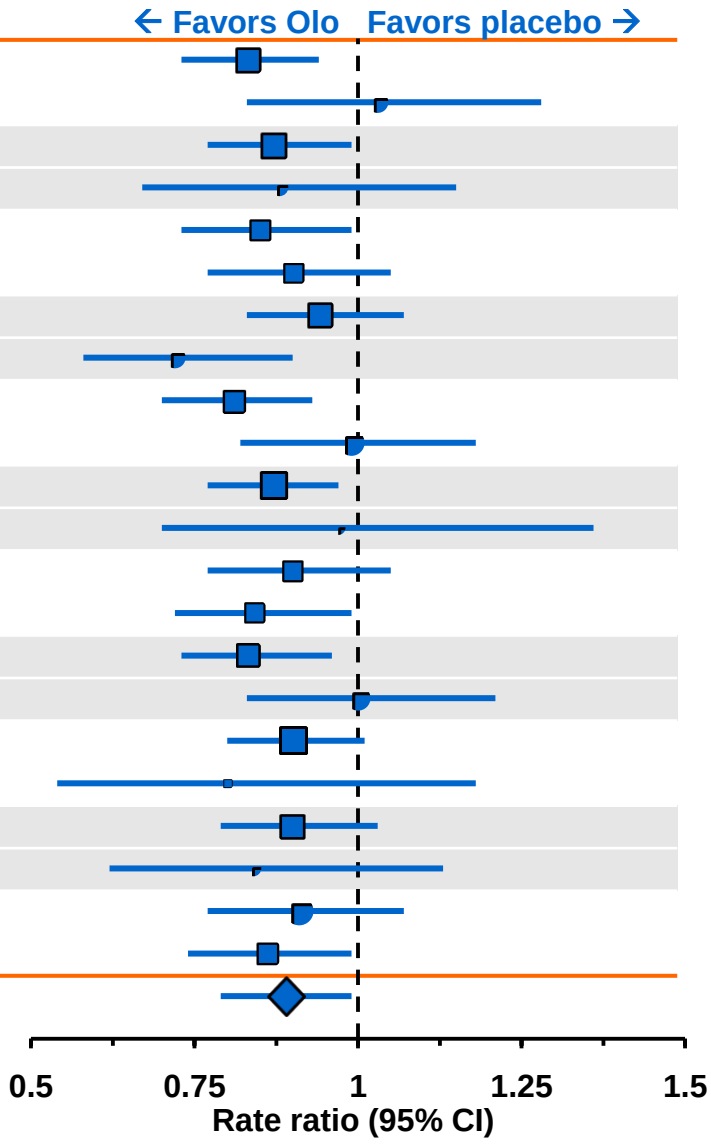
Subgroup	Incidence rate[a] Olo 5 µg	Placebo	Rate ratio (95% CI)
Female	195	213	0.88 (0.70, 1.09)
Male	144	164	0.88 (0.77, 1.00)
Age ≤ 65	150	160	0.93 (0.80, 1.08)
Age > 65	160	192	0.84 (0.71, 0.98)
Asian	121	155	0.77 (0.63, 0.95)
Black	105	211	0.84 (0.34, 2.07)
White	175	184	0.95 (0.83, 1.08)
Asia region	120	156	0.76 (0.62, 0.93)
Europe	186	186	0.99 (0.80, 1.22)
Other	161	177	0.84 (0.65, 1.09)
US	170	188	0.90 (0.72, 1.13)
Current smoker	167	183	0.92 (0.77, 1.10)
Ex-smoker	147	169	0.87 (0.76, 1.00)
GOLD II	159	181	0.88 (0.75, 1.03)
GOLD III	148	169	0.87 (0.72, 1.04)
GOLD IV	162	165	1.02 (0.72, 1.43)
Renal normal	160	166	0.96 (0.81, 1.13)
Renal mild impaired	148	181	0.82 (0.69, 0.97)
Renal moderate impaired	157	189	0.84 (0.59, 1.21)
Renal severe impaired	170	896	0.39 (0.10, 1.57)
No cardiac history	146	167	0.87 (0.77, 0.99)
With cardiac history	183	201	0.87 (0.70, 1.09)
Overall	**154**	**174**	**0.89 (0.79, 0.99)**



[a] Patients with an event per 100 pt-yr.

Adverse Event Exposure-adjusted Rate Ratio—Olodaterol 5 µg vs Placebo

Subgroup	Incidence rate[a] Olo 5 µg	Placebo	Rate ratio (95% CI)
No baseline LAMA	151	182	0.83 (0.73, 0.94)
Had baseline LAMA	202	196	1.03 (0.83, 1.28)
No baseline xanthine	161	184	0.87 (0.77, 0.99)
Had baseline xanthine	166	196	0.88 (0.67, 1.15)
No baseline ICS	147	174	0.85 (0.73, 0.99)
Had baseline ICS	180	200	0.90 (0.77, 1.05)
No baseline SAMA	172	183	0.94 (0.83, 1.07)
Had baseline SAMA	137	193	0.72 (0.58, 0.90)
No baseline LABA	146	180	0.81 (0.70, 0.93)
Had baseline LABA	194	196	0.99 (0.82, 1.18)
No baseline beta-blocker	157	181	0.87 (0.77, 0.97)
Had baseline beta-blocker	220	234	0.97 (0.70, 1.36)
No LAMA or SAMA	160	178	0.90 (0.77, 1.05)
Had LAMA or SAMA	163	194	0.84 (0.72, 0.99)
Not beta agonist reversible	143	171	0.83 (0.73, 0.96)
Beta agonist reversible	181	181	1.00 (0.83, 1.21)
No CPK shift	160	177	0.90 (0.80, 1.01)
Had CPK shift	120	138	0.80 (0.54, 1.18)
No diabetes	173	192	0.90 (0.79, 1.03)
Had diabetes	168	199	0.84 (0.62, 1.13)
Not FEV_1 reversible	145	160	0.91 (0.77, 1.07)
FEV_1 reversible	163	188	0.86 (0.74, 0.99)
Overall	**154**	**174**	**0.89 (0.79, 0.99)**



[a] Patients with an event per 100 pt-yr.

Adverse Events Summary in Phase II Asthma Studies

Studies 4, 6, 27, 29

	Patients, %							
		Olodaterol						Formoterol
	Placebo n = 409	2 µg n = 210	2.5 µg bid n = 101	5 µg n = 319	5 µg bid n = 101	10 µg n = 319	20 µg n = 214	12 µg n = 125
Patients with any AE	**14.9**	**18.1**	**14.9**	**18.5**	**18.8**	**16.3**	**21.5**	**6.4**
Severe AEs	0.2	0.5	1.0	0.9	0	0.6	1.4	0
Investigator-def. related AEs	2.0	1.4	0	2.8	3.0	2.8	5.6	0
Other significant AEs	0.2	0.5	1.0	0.9	1.0	0.6	0	0
AEs leading to discontinuation of trial drug	0.2	0.5	1.0	0.9	1.0	0.6	0	0
Serious AEs[a]	0.5	0	1.0	0	1.0	0.6	0.5	0
Requiring hospitalization	0.5	0	1.0	0	1.0	0.6	0.5	0

[a] **No fatal, life-threatening, disabilitating, prolonging hospitalization, congenital abnormality or other event in any treatment group.**

Summary of Safety of Olodaterol in COPD (1)

- Olodaterol development program included a broad range of moderate to very severe COPD patients
  - Many co-morbidities, state-of-the-art pulmonary and non-pulmonary co-medication
  - Documented safety profile in 1,500 patient-years, relevant for clinical use, including safety in double the proposed dose,
- Rate of treatment discontinuation lower in olodaterol than placebo
- Overall frequency of AEs, SAEs, and deaths balanced across treatment groups
- Pneumonia appeared more frequent in olodaterol 10 µg not 5 µg
  - Inclusive term “key respiratory events” similar across all groups

Summary of Safety of Olodaterol in COPD (2)

- Malignant and unspecified neoplasms numerically more frequent in active treatment groups, lung cancer in olodaterol 10 µg and formoterol
  - Diverse tumor types and locations, as expected for population
  - Review of lung cancer case reports mostly indicates pre-existing disease considering latency period
  - Preclinical investigations do not indicate a mutagenic or carcinogenic potential in man
- ADRs identified, mostly typical for the class: arthralgia, hypertension, dizziness, nasopharyngitis, rash
- No overall safety concerns in any patient subgroup or co-medication subgroup

➔ Substantial evidence for safety of olodaterol; offers a positive benefit to risk as once-daily LABA in patients with COPD

Components of Olodaterol Risk Management

- Appropriate product information and labeling
  - Medication guide, minimize off-label use
- Pharmacovigilance
  - Continuous safety screening
  - Signal detection (BI database, FDA AERS database)
  - Large, ongoing program of combination development will extend safety database in COPD (5,000 patients)
- REMS
  - Communication plan
  - REMS assessment

Clinical Summary and Perspective on the Use of Olodaterol for Patients With COPD

Richard Casaburi, PhD, MD

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UCLA School of Medicine
Medical Director, Rehabilitation Clinical Trials Center
Los Angeles Biomedical Research Institute at
Harbor-UCLA Medical Center

GOLD Guidelines—COPD Therapeutic Goals

- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat exacerbations
- Prevent disease progression
- Reduce mortality

Olodaterol Addresses Important Therapeutic Goals: *Effective Bronchodilation*

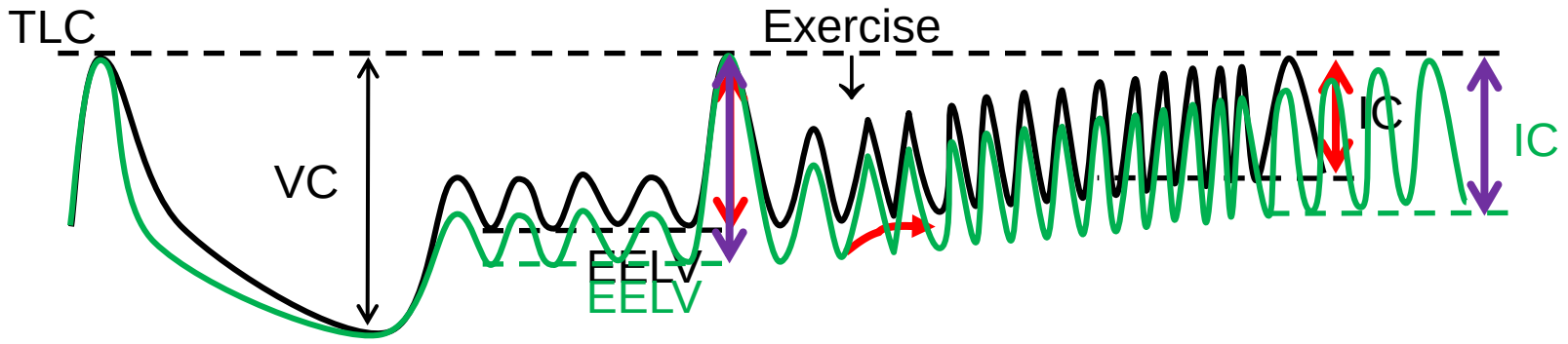
- Rapid onset of action
  - FEV_1 increase at 5 minutes was clinically meaningful
- Sustained improvement in lung function
  - 24-hr bronchodilation
  - FEV_1 AUC_{0-3}
    - 0.162 L (pivotal studies); 0.211 L (24-hr PFT studies)
  - Trough FEV_1
    - 0.071 L (pivotal studies); 0.134 L (24-hr PFT studies)
- Improved lung function in pivotal studies observed against a background of concomitant therapy
  - LAMA, SAMA, ICS, xanthines

Olodaterol Addresses Important Therapeutic Goals: *Symptomatic Benefit*

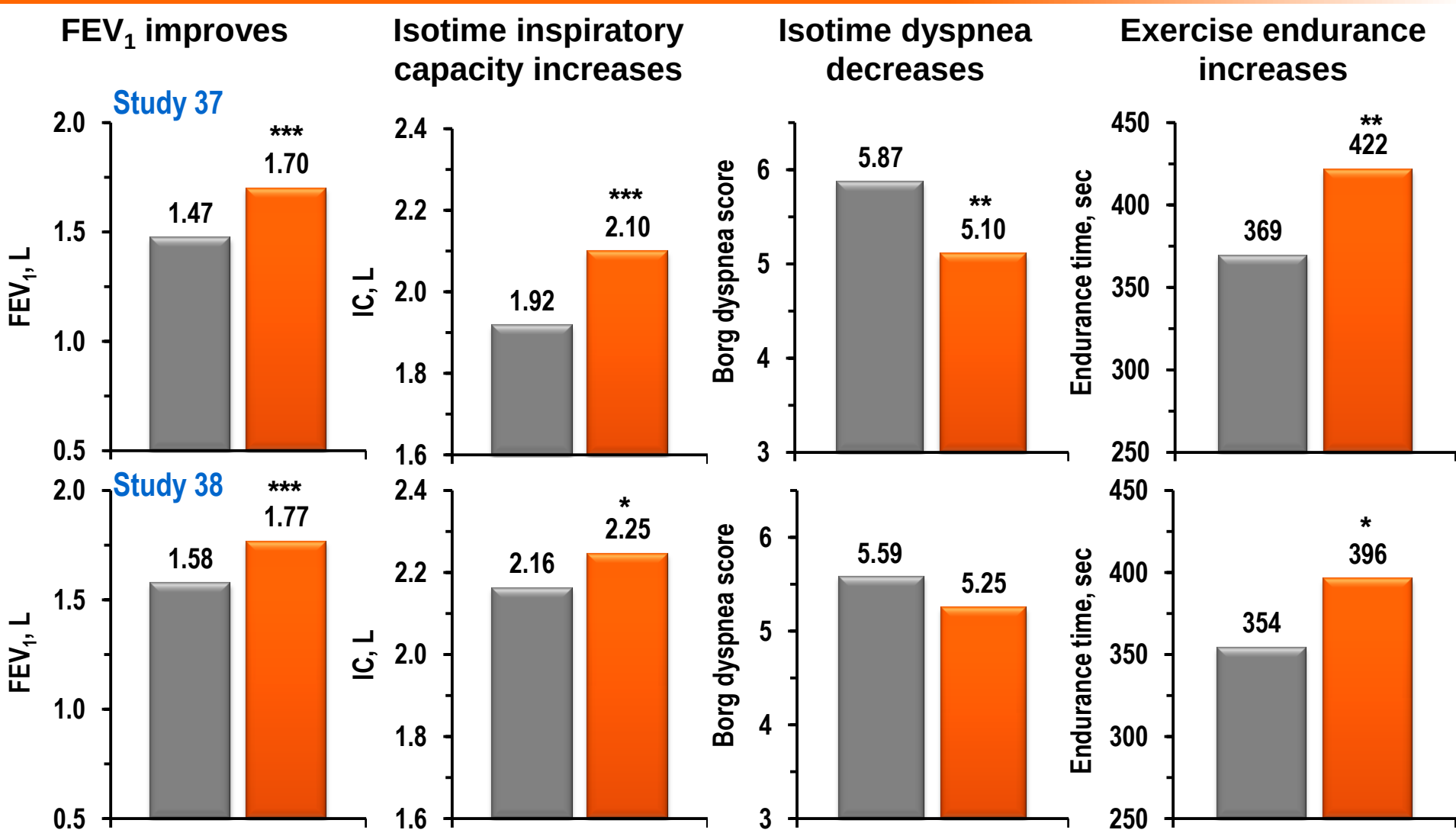
- Reduced rescue medication use
  - 20% to 30% reduction in rescue albuterol use
- Improved health-related QoL
  - Nominally statistically significant SGRQ Total Score reduction in Study 13/14 combined dataset, although MCID was not reached
- Trend toward reduction in dyspnea scores

Olodaterol Addresses Important Therapeutic Goals: *Improved Exercise Tolerance*

- Substantial evidence from two, 6-week, randomized, double-blind, placebo-controlled, cross-over exercise studies
- Double-blinding and cross-over design reduce the influence of psychological and other non-COPD-related factors on results
- Demonstrates linkage of improved airflow to reduced lung hyperinflation and dyspnea during exercise and thereby, to improved exercise tolerance



Olodaterol Addresses Important Therapeutic Goals: *Improved Exercise Tolerance*



* $p < 0.05$; ** $p < 0.001$; *** $p < 0.0001$.

Olodaterol Addresses Important Therapeutic Goals: *Improved Exercise Tolerance*

- Including exercise tolerance data in a product label allows for a more meaningful discussion of therapeutic benefit with patients
  - Physicians work with patients to identify appropriate management of the patient's COPD
  - Communication should be based on concepts important to the patient
  - Exercise tolerance improvement, which is a consequence of improving airflow limitation, is easily understood

Olodaterol Development Program: *Providing Clinical Relevance*

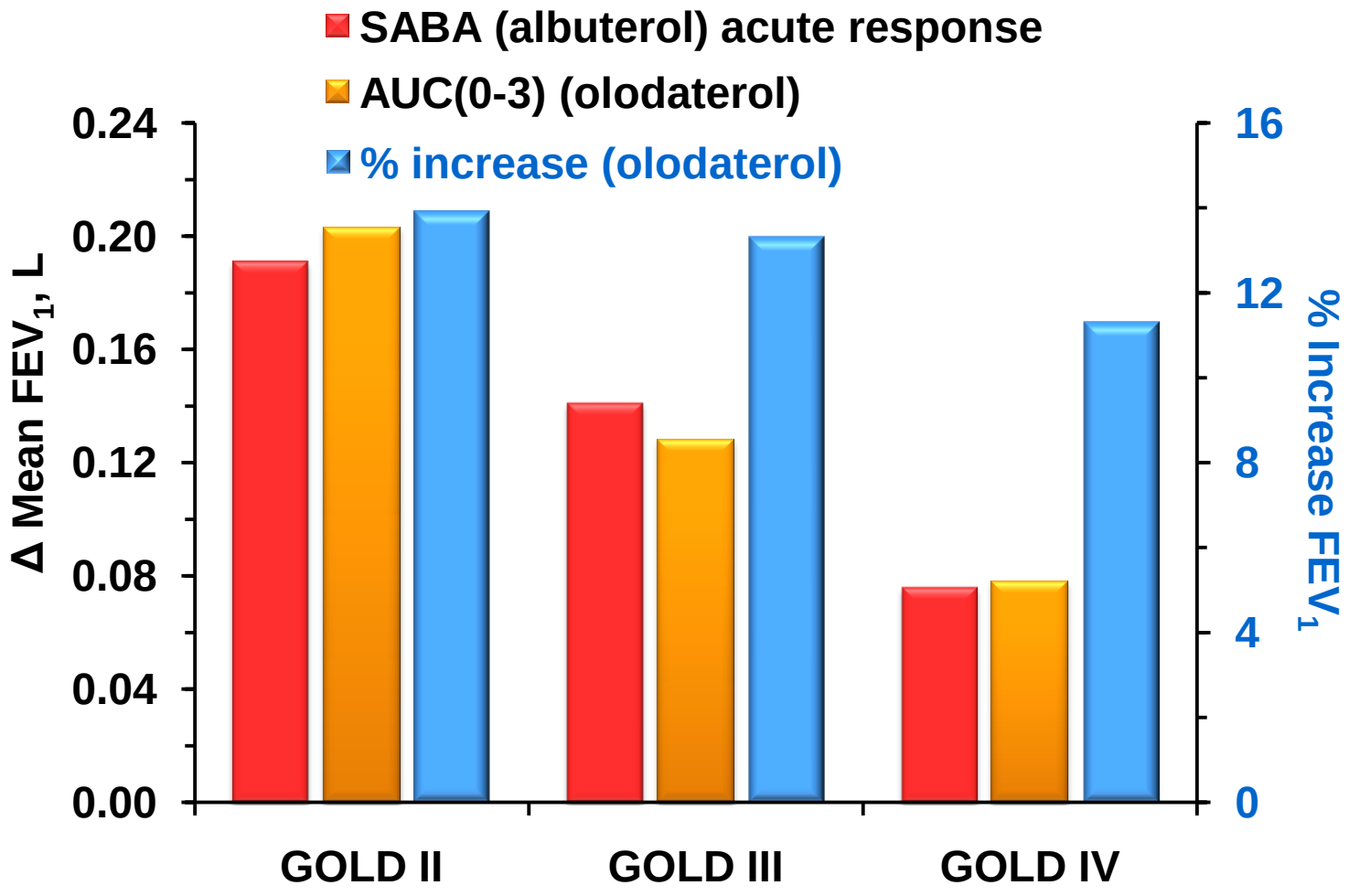
- Effective in a broad population
- Well-characterized safety profile
- Easy-to-use delivery system

Olodaterol Development Program: *Providing Clinical Relevance: Effectiveness*

- Studied in a broad cross-section of patients
  - Full range of disease severity
  - Background of co-morbidities and relevant concomitant medications
- An alternative therapy
  - Potential to combine with other therapies in the future
- Effect size meets expectations for population
  - Disease severity
  - Background bronchodilators

FEV_1 AUC_{0-3} Response Compared With SABA Response Across GOLD Stages

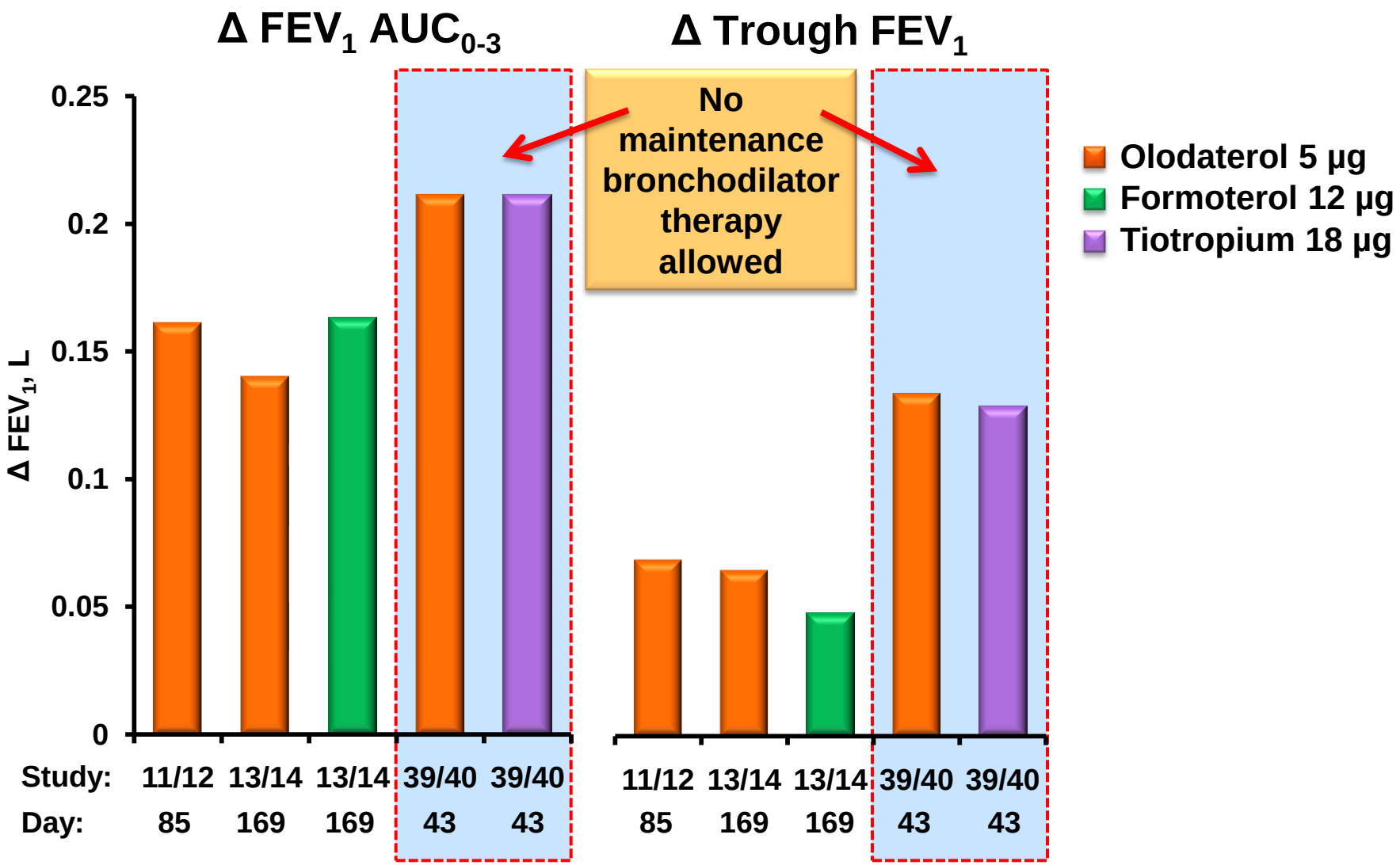
Pooled Dataset for Studies 11-14



Background Maintenance Bronchodilator Therapy Influences Response to Olodaterol

CP-11

Studies 11/12, 13/14, and 39/40



Olodaterol Development Program: *Providing Clinical Relevance: Safety*

- Safety is well characterized
  - Safety data derived from 48-week studies
  - Extensive safety database
    - 28 studies
    - 4,329 patients with COPD
    - Four 48-week, double-blind, placebo-controlled studies (N = 3,104)
  - Data for both 5 µg and 10 µg doses in clinical trials

Olodaterol Development Program: *Providing Clinical Relevance: Convenience*

- Once-daily dosing
- RESPIMAT device
  - A multi-dose inhaler that generates slow-moving mist and reduces the need to coordinate inhalation
  - Dose indicator

Examples of Patients Who Would Benefit From Olodaterol

- 50-year-old COPD patient with occasionally bothersome symptoms and low risk of exacerbations but not adequately controlled on short-acting bronchodilators
- 65-year-old COPD patient on maintenance anticholinergic therapy who continues to have symptoms including compromised exercise tolerance and needs additional maintenance bronchodilator

Conclusion

- Olodaterol was studied in 10 Phase III trials that demonstrated improved lung function in patients with moderate to very severe COPD
  - Clinically meaningful improvement in lung function in context of bronchodilator background therapy
  - Improved exercise tolerance time
- Well characterized safety profile at 5 µg and 10 µg doses
- Olodaterol will enhance clinician's armamentarium of COPD therapies
  - Once-daily bronchodilator
  - Multi-dose alternative delivery system

Supportive Data

Locus of Symptom Limitation Questionnaire

1) Did you stop exercising because of:
   - Discomfort with your legs?
   - Discomfort with your breathing?
   - Both discomfort with your legs and discomfort with your breathing?
   - None of the above

2) Did you stop exercising because of pain in your chest?
   Yes ☐ No ☐

3) Did you stop exercising for any other reason?
   Yes ☐ No ☐

If you answered “yes” to question 3, describe the reason:

Contraindications to Exercise

ERS Task Force on Standardization of Clinical Exercise Testing[a]

Absolute

- Acute myocardial infarction (3-5 days)
- Unstable angina
- Uncontrolled arrhythmias causing symptopms of hemodynamic compromise
- Active endocarditis
- Acute myocarditis or pericarditis
- Symptomatic severe aortic stenosis
- Uncontrolled heart failure
- Acute pulmonary embolus or pulmonary infarction
- Acute noncardiac disorder that may affect exercise performance or be aggravated by exercise (ie, infection, renal failure, thyrotoxicosis)
- Thrombosis of lower extremities

Relative

- Left main coronary stenosis or its equivalent
- Moderate stenotic valvular heart disease
- Electrolyte abnormalities
- Severe untreated arterial hypertension (> 200 mmHg systolic, > 120 mmHg diastolic)
- Significant pulmonary hypertension
- Tachyarrhythmias or bradyarrhythmias
- Hypertrophic cardiomyopathy
- Mental impairment leading to inability to cooperate
- High degree of atrioventricular block

[a] **ERS Task Force. *Eur Respir J*. 1997;10:2662-2689.**

Drug Delivery With the Respimat Inhaler

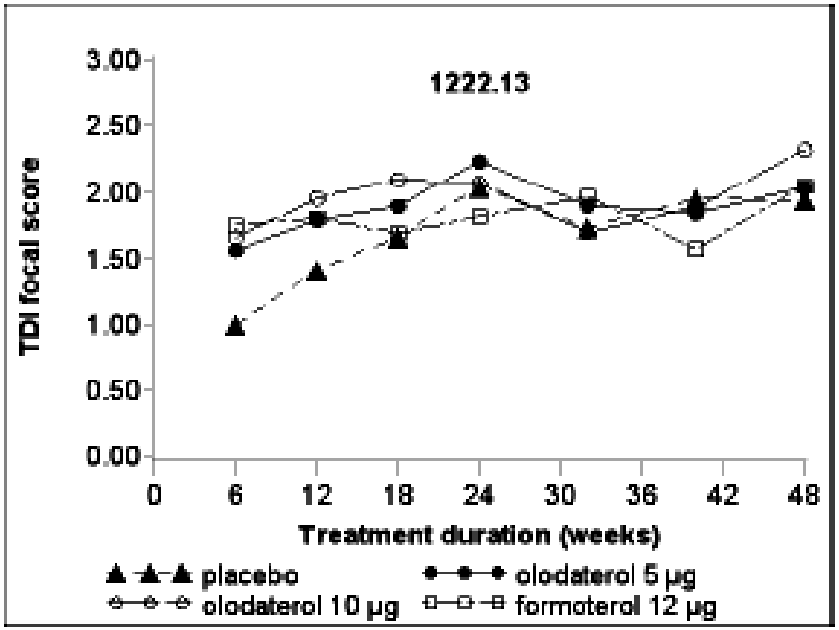
Distribution of radioactivity

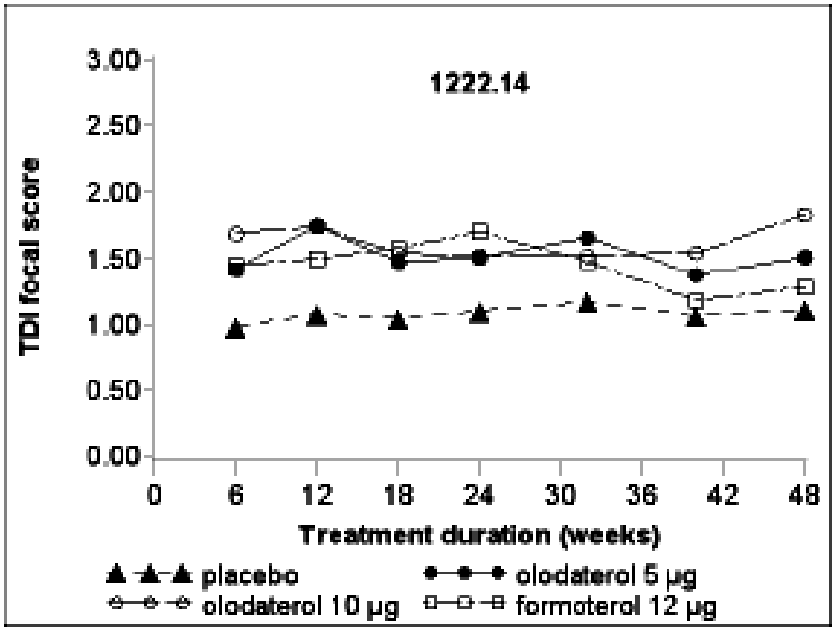
Device	22%	(CV: 28%)
Lung	39%	(CV: 32%)
Oropharynx	37%	(CV: 28%)
Exhaled	2%	(CV: 89%)

Data from γ-scintigraphy study with aqueous fenoterol solution
(Newman *et al.*, 1998, Chest 113 (4), 957-963)

TDI Focal Scores—48 Weeks

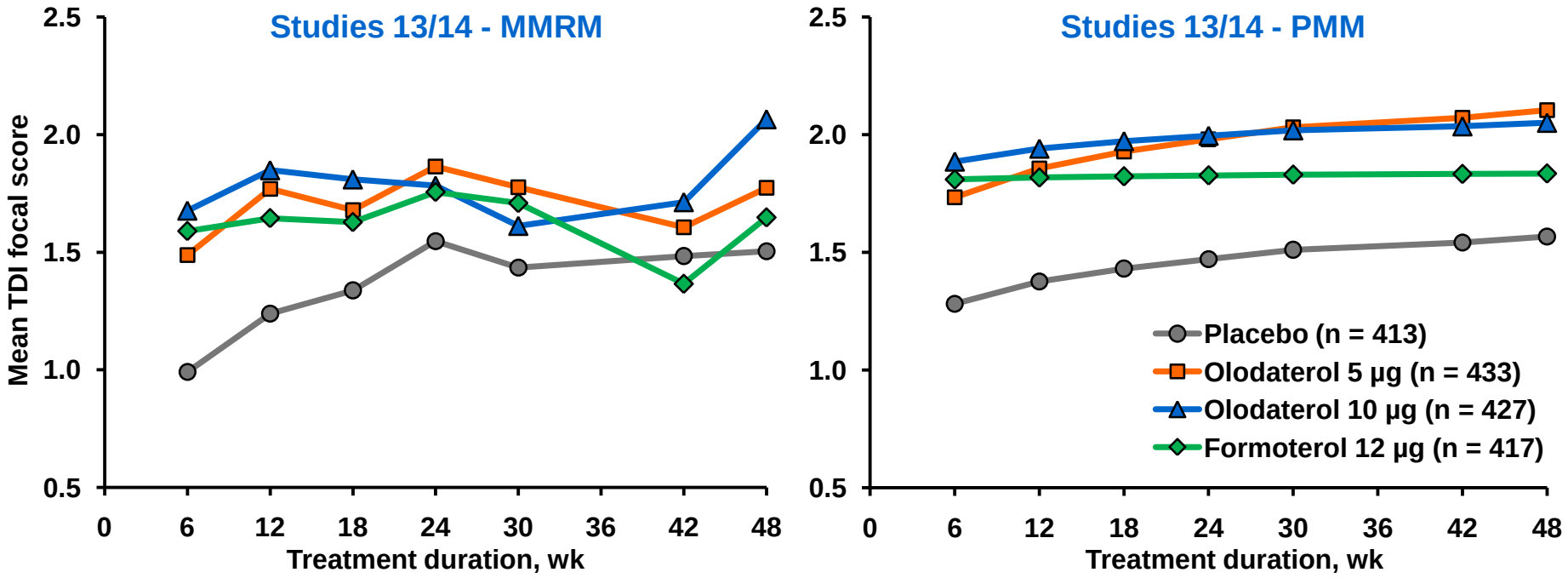
Studies 13 and 14





Source data: [SCE, Figure 3.2.2.1: 1]

Transition Dyspnea Index (TDI) Focal Score



Common baseline mean (SE)

Comorbidities (> 3%)
Studies 37, 38 Combined

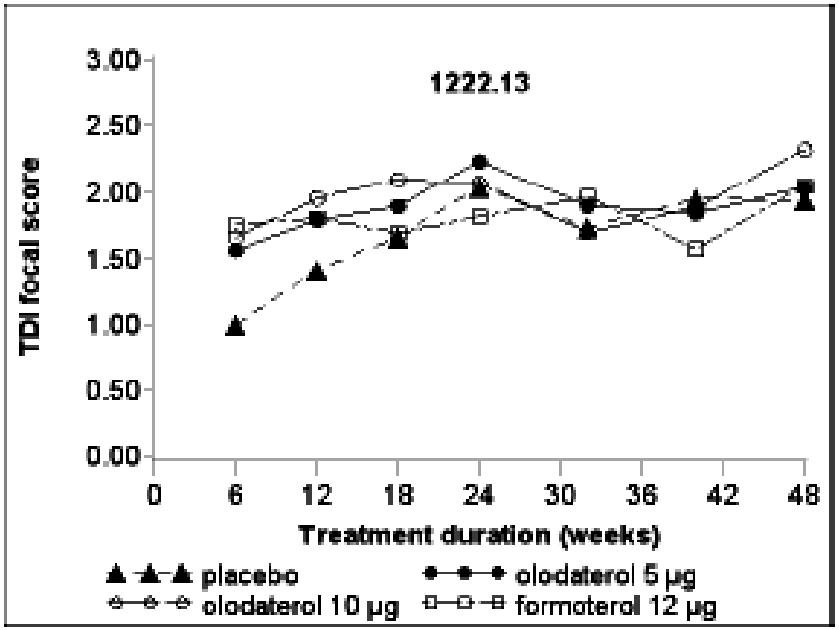
	Patients, n (%)
Number of patients	308
Bundle branch block rt	15 (4.9)
Myocardial Infarction	12 (3.9)
Myocardial Ischemia	13 (4.2)
Gastritis	20 (6.5)
Gastroesophageal reflux disease	23 (7.5)
Diabetes Mellitus	15 (4.9)
Gout	10 (3.2)
Hypercholesterolemia	55 (17.9)
Hyperlipidemia	17 (5.5)
Hyperuricemia	15 (4.9)
Obesity	29 (9.4)
Type 2 Diabetes Mellitus	10 (3.2)
Arthritis	10 (3.2)
Back Pain	11 (3.6)
Osteoarthritis	19 (6.2)
Osteoporosis	21 (6.8)
Depression	28 (9.1)
Benign prostatic hyperplasia	11 (3.6)
Sleep apnea syndrome	15 (4.9)
Menopause	10 (3.2)
Postmenopause	14 (4.5)
Hysterectomy	10 (3.2)
Hypertension	132 (42.9)

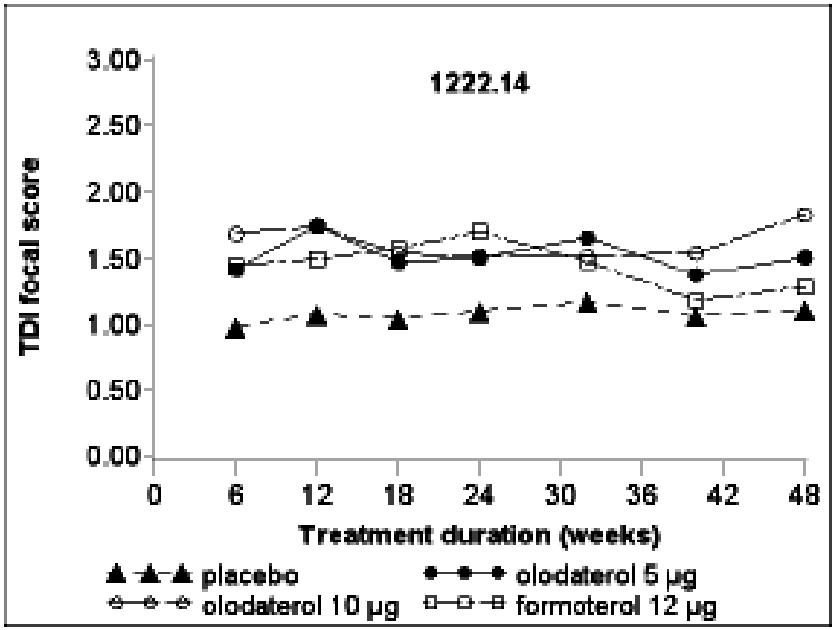
Baseline Body Mass Index > 28 kg/m^2 Studies 37, 38 Combined

	Total N = 303
BMI > 28 kg/m^2	
N	118 (38)

TDI Focal Scores—48 Weeks

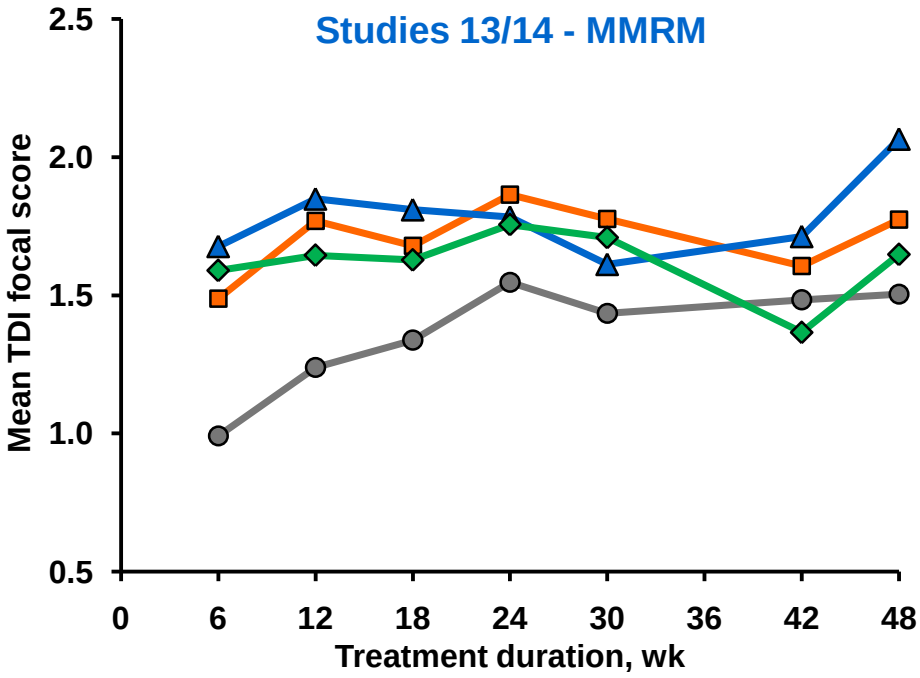
Studies 13 and 14

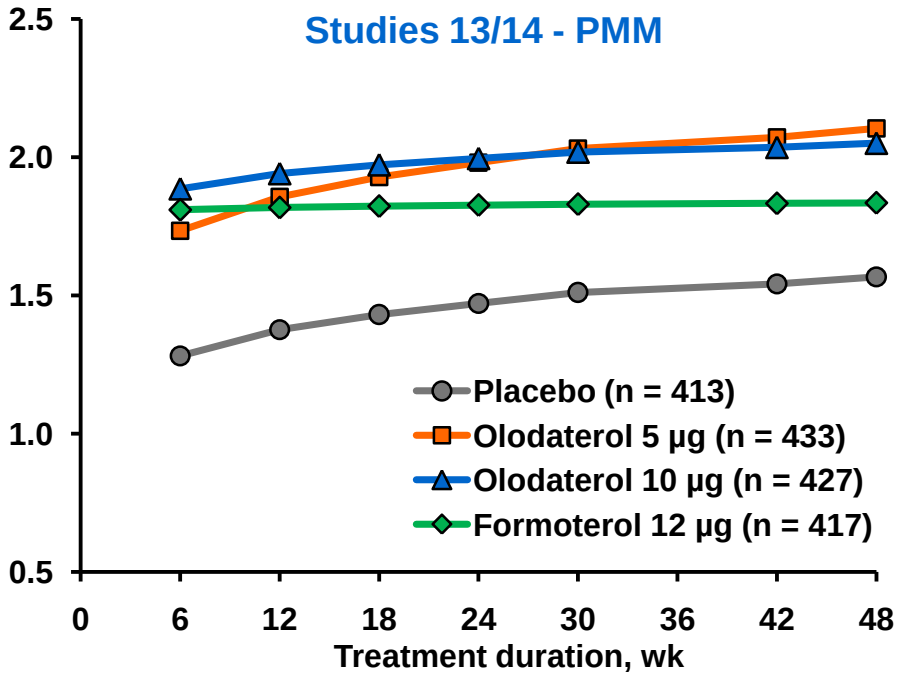




Source data: [SCE, Figure 3.2.2.1: 1]

Transition Dyspnea Index (TDI) Focal Score



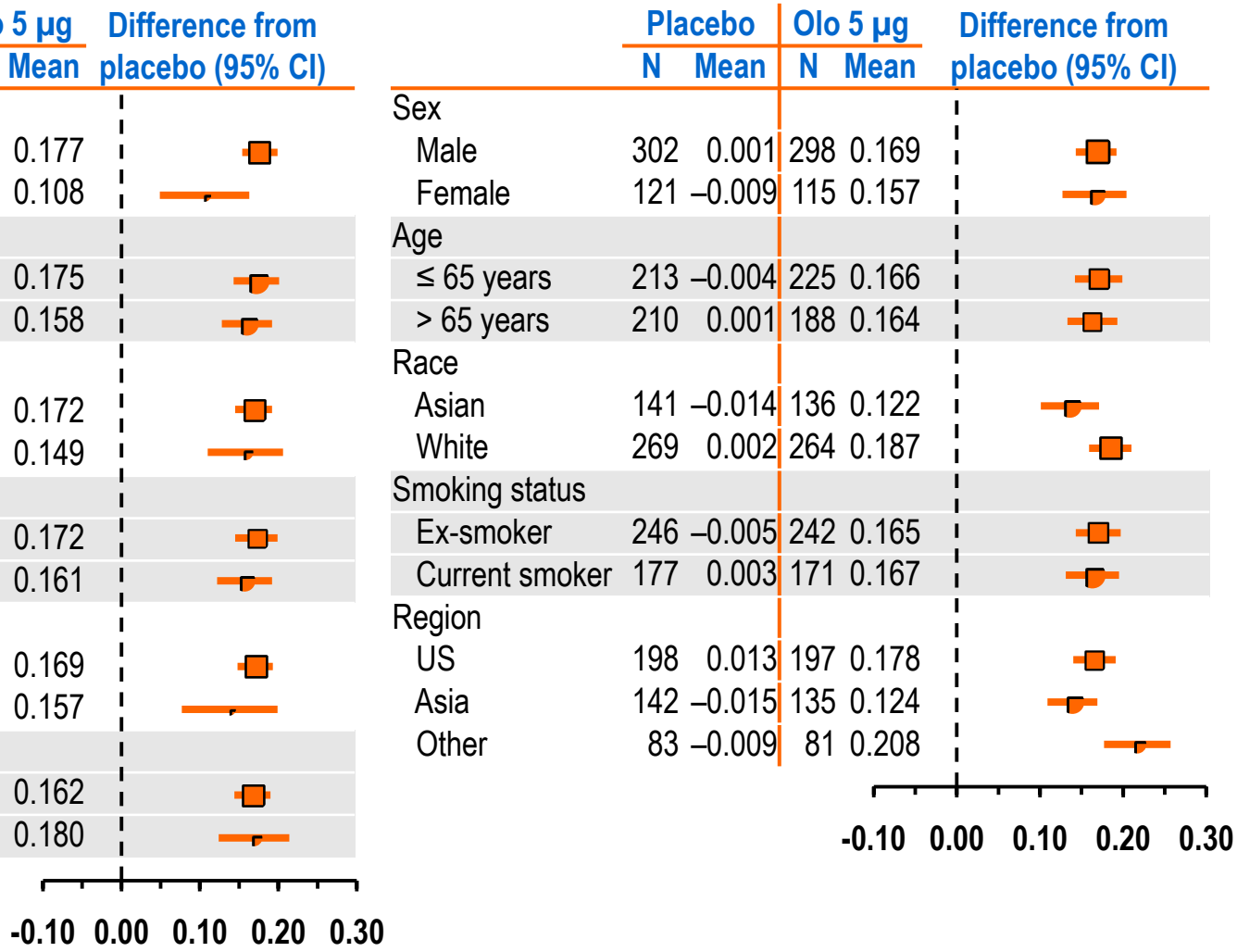


Common baseline mean (SE)

FEV_1 AUC_{0-3} Response by Baseline Demographics

Studies 11/12 Combined Dataset

	Placebo N	Placebo Mean	Olo 5 µg N	Olo 5 µg Mean
Concomitant xanthine				
No	345	0.001	337	0.177
Yes	56	0.002	53	0.108
Concomitant ICS				
No	221	0.003	218	0.175
Yes	180	–0.002	172	0.158
Concomitant SAMA				
No	317	0.004	315	0.172
Yes	84	–0.009	75	0.149
LABA prior to entry				
No	255	–0.000	246	0.172
Yes	146	0.004	144	0.161
Beta blocker at BL				
No	354	–0.001	339	0.169
Yes	47	0.019	51	0.157
Tiotropium stratum				
Non-tiotropium	333	–0.005	327	0.162
Tiotropium	90	0.011	86	0.180
Sex				
Male	302	0.001	298	0.169
Female	121	–0.009	115	0.157
Age				
≤ 65 years	213	–0.004	225	0.166
> 65 years	210	0.001	188	0.164
Race				
Asian	141	–0.014	136	0.122
White	269	0.002	264	0.187
Smoking status				
Ex-smoker	246	–0.005	242	0.165
Current smoker	177	0.003	171	0.167
Region				
US	198	0.013	197	0.178
Asia	142	–0.015	135	0.124
Other	83	–0.009	81	0.208

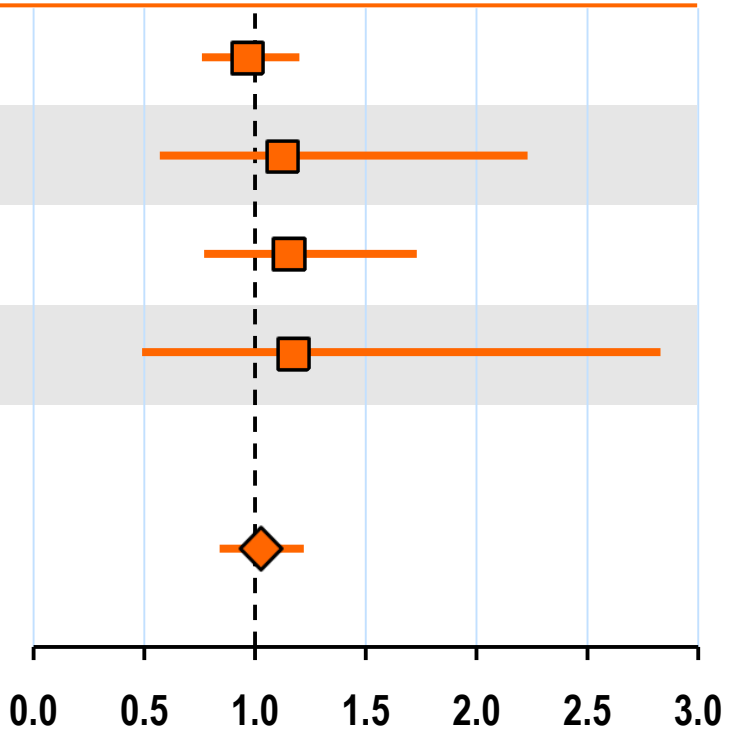


Pattern Mixture Model in Olodaterol

- Pattern mixture model (PMM)
  - Assumes that patients who complete the study and those who do not complete have different patterns and have different effect sizes.
  - The overall effect is produced by the weighted mean of these effect sizes.
- PMM in olodaterol project: Statistics in Medicine, Tutorial in Biostatistics (2004) – Hogan and others
  - Patients grouped together based on time to discontinuation (patterns)
  - Fit a regression (random slope and intercept) model over time for each pattern of discontinuation
  - Develop a weighted mean of regression coefficients
  - Calculate means for each treatment group based on the predicted value at a given time point (eg, Day 169)
  - Compare treatment means

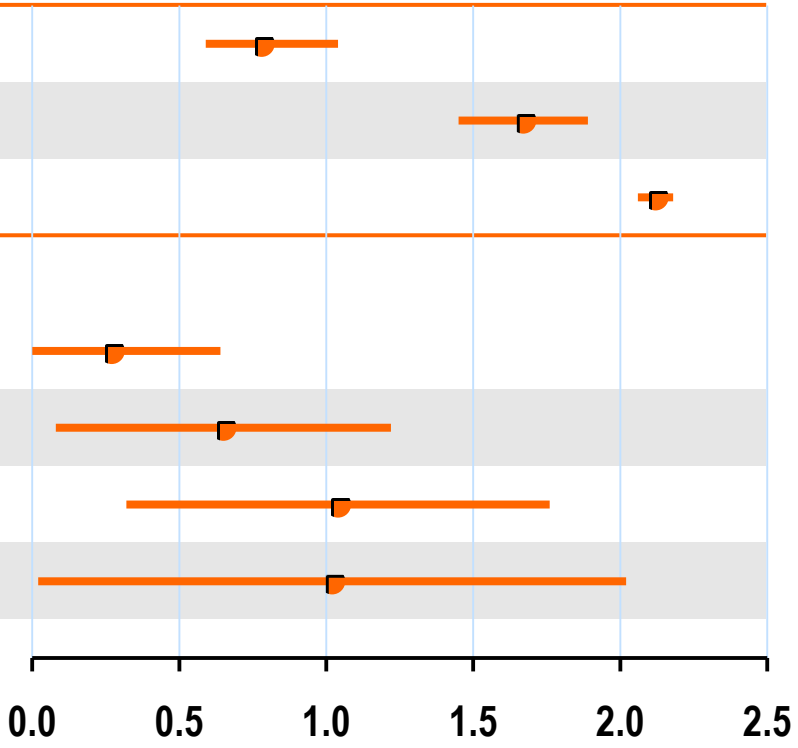
Rate Ratio of Neoplasm SAE for LABA vs No LABA From RCTs in COPD

	LABA		No LABA	
	Cases	Person-yr	Cases	Person-yr
TORCH (salmeterol)	152	7231	150	6833
INSPIRE (salmeterol)	18	1011	15	946
POET (salmeterol)	43	3496	51	3592
Indacaterol 12-mo trials	17	1152	7	556
Overall				



Incidence Rate of Lung Cancer per 100/Yr

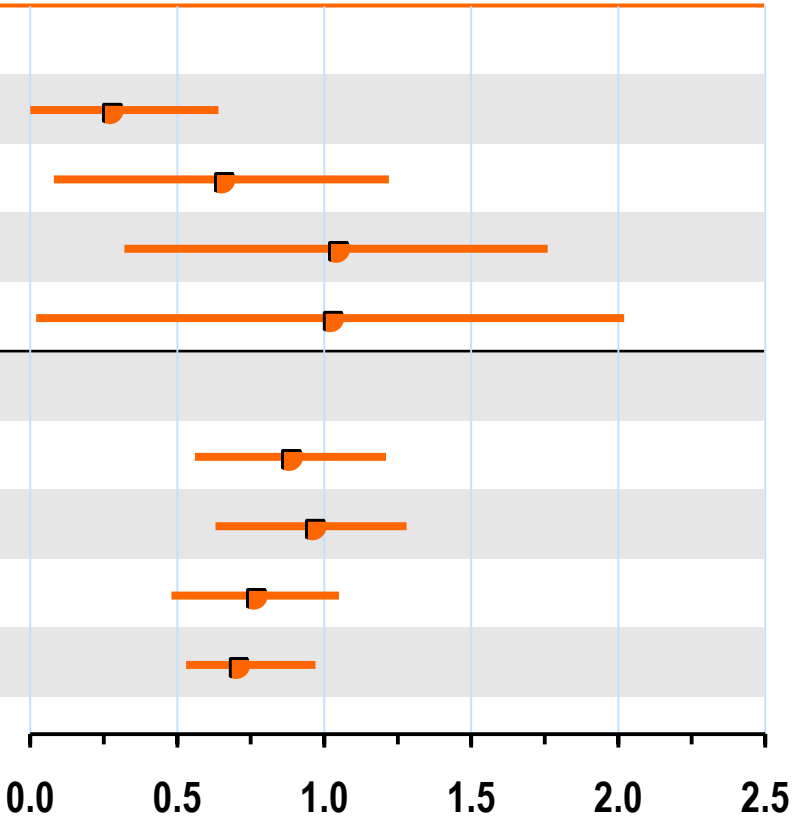
	Cases	Person-yr
Rodriguez 2010	48	6,153
De Torres 2011	215	12,874
Kornum 2012	4,209	198,585
48-week trials		
Placebo	2	741
Olodaterol 5 µg	5	769
Olodaterol 10 µg	8	769
Formoterol 12 µg	4	392



Torres Jd, et al. *Am J Respir Crit Care Med*. 2011;184:913-919.
Rodriguez LA, et al. *Respir Med*. 2010;104:1691-1699.
Kornum JB, et al. *Respir Med*. 2012;106:845-852.

Incidence Rate of Lung Cancer per 100/Yr

	Cases	Person-yr
48-week trials		
Placebo	2	741
Olodaterol 5 µg	5	769
Olodaterol 10 µg	8	769
Formoterol 12 µg	4	392
TORCH		
Placebo	29	3278
Fluticasone	34	3555
Salmeterol	27	3431
Salmeterol+fluticasone	26	3700



Adverse Events in African Americans

48-week Studies in COPD

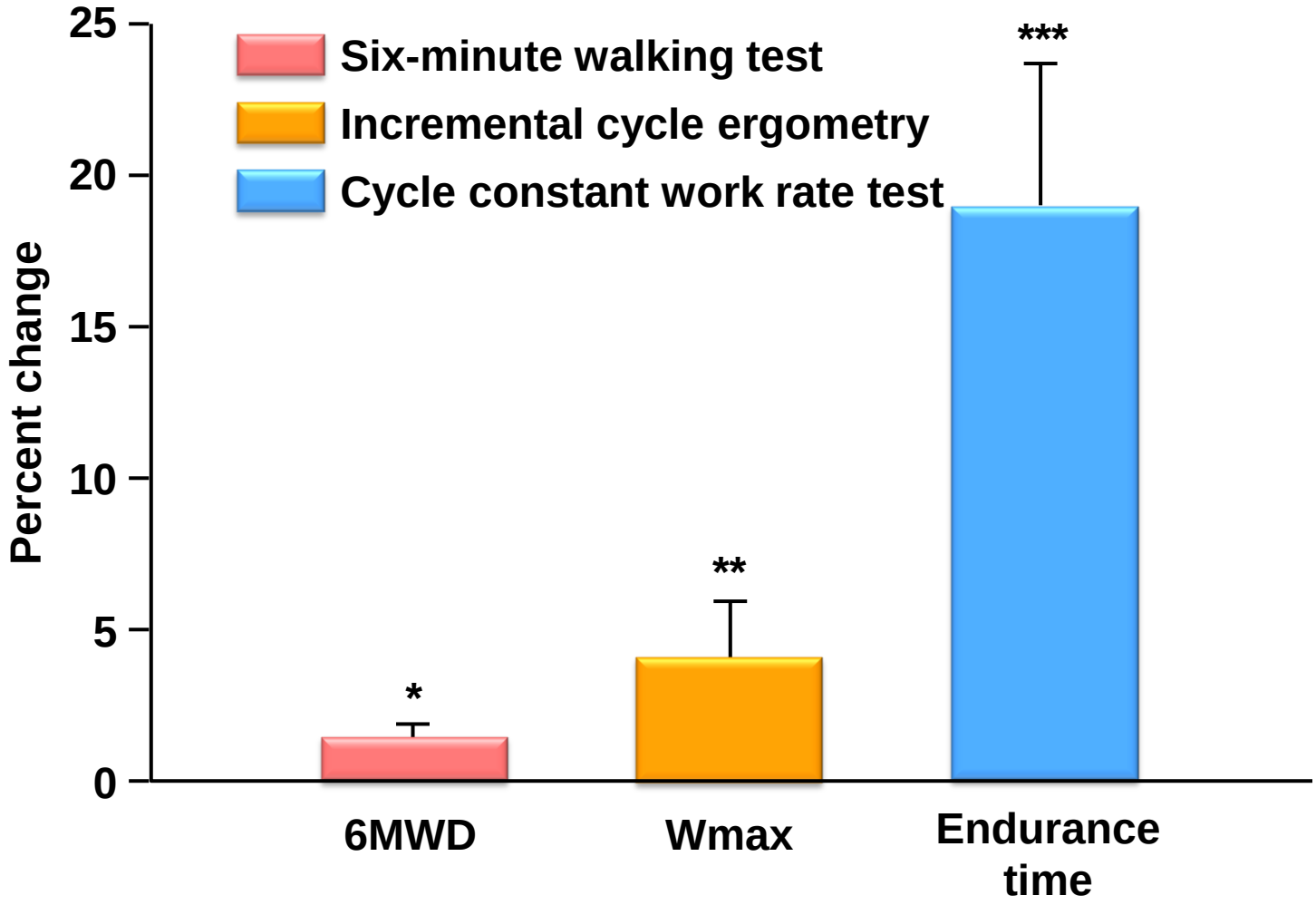
System organ class	Patients, n (%)			
	Placebo	Olo 5 µg	Olo 10 µg	Form 12 µg
All Patients with AEs (%)	**70.8**	**71.0**	**72.7**	**69.1**
Number of patients	11 (100.0)	13 (100.0)	13 (100.0)	2 (100.0)
Total with adverse events	9 (81.8)	8 (61.5)	9 (69.2)	2 (100.0)
Infections and infestations	5 (45.5)	4 (30.8)	2 (15.4)	0
Metabolism and nutrition disorders	2 (18.2)	0	3 (23.1)	0
Psychiatric disorders	1 (9.1)	0	2 (15.4)	0
Nervous system disorders	0	1 (7.7)	2 (15.4)	0
Cardiac disorders	1 (9.1)	1 (7.7)	1 (7.7)	0
Vascular disorders	2 (18.2)	1 (7.7)	1 (7.7)	0
Respiratory, thoracic and mediastinal disorders	5 (45.5)	3 (23.1)	4 (30.8)	1 (50.0)
Gastrointestinal disorders	1 (9.1)	4 (30.8)	2 (15.4)	0
Skin and subcutaneous tissue disorders	0	0	2 (15.4)	0
Musculoskeletal and connective tissue disorders	1 (9.1)	0	0	0
General disorders and administration site conditions	1 (9.1)	1 (7.7)	2 (15.4)	0
Investigations	1 (9.1)	2 (15.4)	0	0
Injury, poisoning and procedural complications	1 (9.1)	2 (15.4)	1 (7.7)	1 (50.0)
Surgical and medical procedures	0	1 (7.7)	0	0

Safety Overview Asian Subgroup

48-week Studies in COPD

MedDRA-defined SOC	Patients, %			
	Placebo n = 285	Olodaterol 5 µg n = 381	Olodaterol 10 µg n = 284	Formoterol 12 µg n = 140
Total with AEs, n (%)	**200 (70.2)**	**177 (63.0)**	**194 (68.3)**	**104 (74.3)**
Infections and infestations	34.0	32.0	29.9	34.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0.7	1.8	1.8	2.1
Blood and lymphatic system disorders	0.4	0.7	0	1.4
Immune system disorders	0	0.4	0.4	0.7
Metabolism and nutrition	3.5	2.8	3.2	1.4
Psychiatric disorders	1.8	2.5	2.1	0
Nervous system disorders	7.4	3.9	8.1	7.1
Eye disorders	4.2	3.2	3.9	2.9
Ear and labyrinth disorders	0.7	0.7	0.7	0.7
Cardiac disorders	7.0	3.9	4.2	2.9
Vascular disorders	1.4	2.1	3.9	2.1
Respiratory, thoracic and mediastinal disorders	44.9	34.2	40.8	40.7
Gastrointestinal disorders	14.0	12.1	12.0	15.7
Hepatobiliary disorders	1.4	1.1	0.7	0
Skin and subcutaneus tissue disorders	3.2	1.4	5.6	5.0
Musculoskeletal and connective tissue disorders	6.0	8.5	10.2	15.0
Renal and urinary disorders	2.1	2.5	2.1	2.9
Reproductive system and breast disorders	0.4	3.2	1.1	0.7
Congenital, familial and genetic disorders	0	0	0.4	0
General disorders and administration site conditions	9.8	8.5	12.0	13.6
Investigations	2.1	1.8	2.5	5.7

Assessing Exercise Tolerance—Constant Work Rate Testing



Changes in various measures of exercise performance after oxitropium bromide in 3 exercise tests. Changes are expressed as the percent change from placebo. Values are expressed as mean ± SE.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
Adapted from Oga (2000)

Responder Analysis
46 sec Threshold

	Treatment	Responders, n (%)	Ratio to placebo		
			Odds ratio (SE)	*p* value	95% CI
Study 37	Placebo	38 (27.7)			
	Olo 5 ug	53 (37.6)	1.57 (0.330)	0.0331	(1.037, 2.374)
	Olo 10 ug	49 (35.8)	1.45 (0.309)	0.0823	(0.953, 2.208)
Study 38	Placebo	45 (30.8)			
	Olo 5 ug	59 (41.8)	1.62 (0.302)	0.0110	(1.117, 2.334)
	Olo 10 ug	58 (41.4)	1.59 (0.326)	0.0253	(1.059, 2.379)

Lower limit for MID range Cazzola M, et al. *Eur Respir J*. 2008:31:416-468.

Responder Analysis
105 sec Threshold

	Treatment	Responders, n (%)	Ratio to placebo		
			Odds ratio (SE)	*p* value	95% CI
Study 37	Placebo	18 (13.1)			
	Olo 5 ug	36 (25.5)	2.27 (0.642)	0.0042	(1.297, 3.960)
	Olo 10 ug	35 (25.5)	2.27 (0.663)	0.0054	(1.276, 4.033)
Study 38	Placebo	28 (19.2)			
	Olo 5 ug	42 (29.8)	1.79 (0.368)	0.0051	(1.192, 2.681)
	Olo 10 ug	35 (25.0)	1.40 (0.324)	0.1422	(0.892, 2.213)

Upper limit for MID range Cazzola M, et al. *Eur Respir J*. 2008:31:416-468.

Mean IC Response [L] After 6 Weeks (Body Box) SD-21

Studies 37 and 38

Study 37			Treatment	Difference from placebo		
Planned time	Treatment	N	mean (SE)	Mean (SE)	*p* value	95% CI
-0:30	Placebo	135	2.170 (0.040)			
	Olo 5ug	140	2.289 (0.040)	0.119 (0.034)	0.0005	(0.052, 0.185)
	Olo 10ug	134	2.262 (0.040)	0.092 (0.034)	0.0073	(0.025, 0.159)
1:00	Placebo	135	2.221 (0.040)			
	Olo 5ug	140	2.427 (0.040)	0.206 (0.035)	< 0.0001	(0.136, 0.275)
	Olo 10ug	134	2.437 (0.040)	0.216 (0.036)	< 0.0001	(0.146, 0.285)

Study 38			Treatment	Difference from placebo		
Planned time	Treatment	N	mean (SE)	Mean (SE)	*p* value	95% CI
-0:30	Placebo	147	2.463 (0.041)			
	Olo 5ug	146	2.613 (0.041)	0.150 (0.040)	0.0002	(0.071, 0.228)
	Olo 10ug	142	2.618 (0.042)	0.154 (0.040)	0.0001	(0.076, 0.233)
1:00	Placebo	147	2.493 (0.040)			
	Olo 5ug	146	2.725 (0.040)	0.232 (0.036)	< 0.0001	(0.162, 0.303)
	Olo 10ug	142	2.696 (0.040)	0.203 (0.036)	< 0.0001	(0.133, 0.273)

Based on a mixed effects repeated measures model. The model includes treatment, baseline endurance time, period treatment as fixed effects and patient as a random effect, along with compound symmetry as a covariance structure for within−patient variation.

Common baseline mean: Study 37 = 2.286 (0.056); Study 38 = 2.503 (0.062)